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INTERNAL MEDICINE

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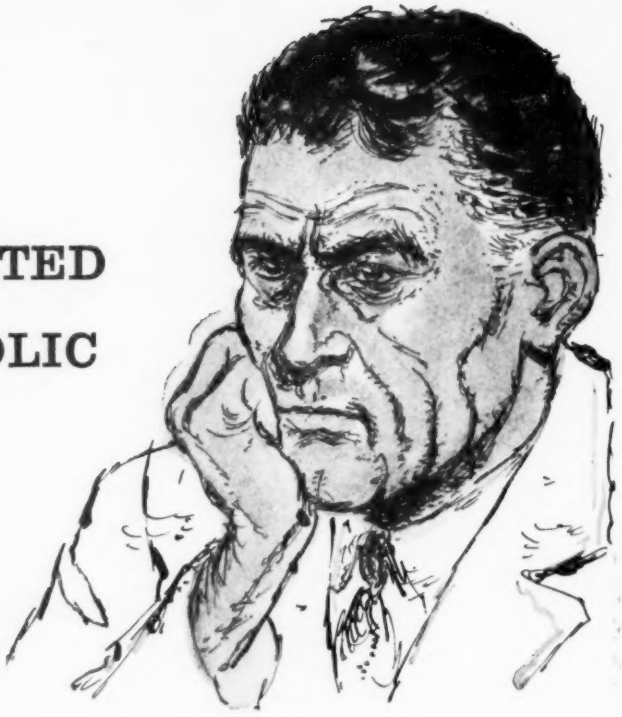

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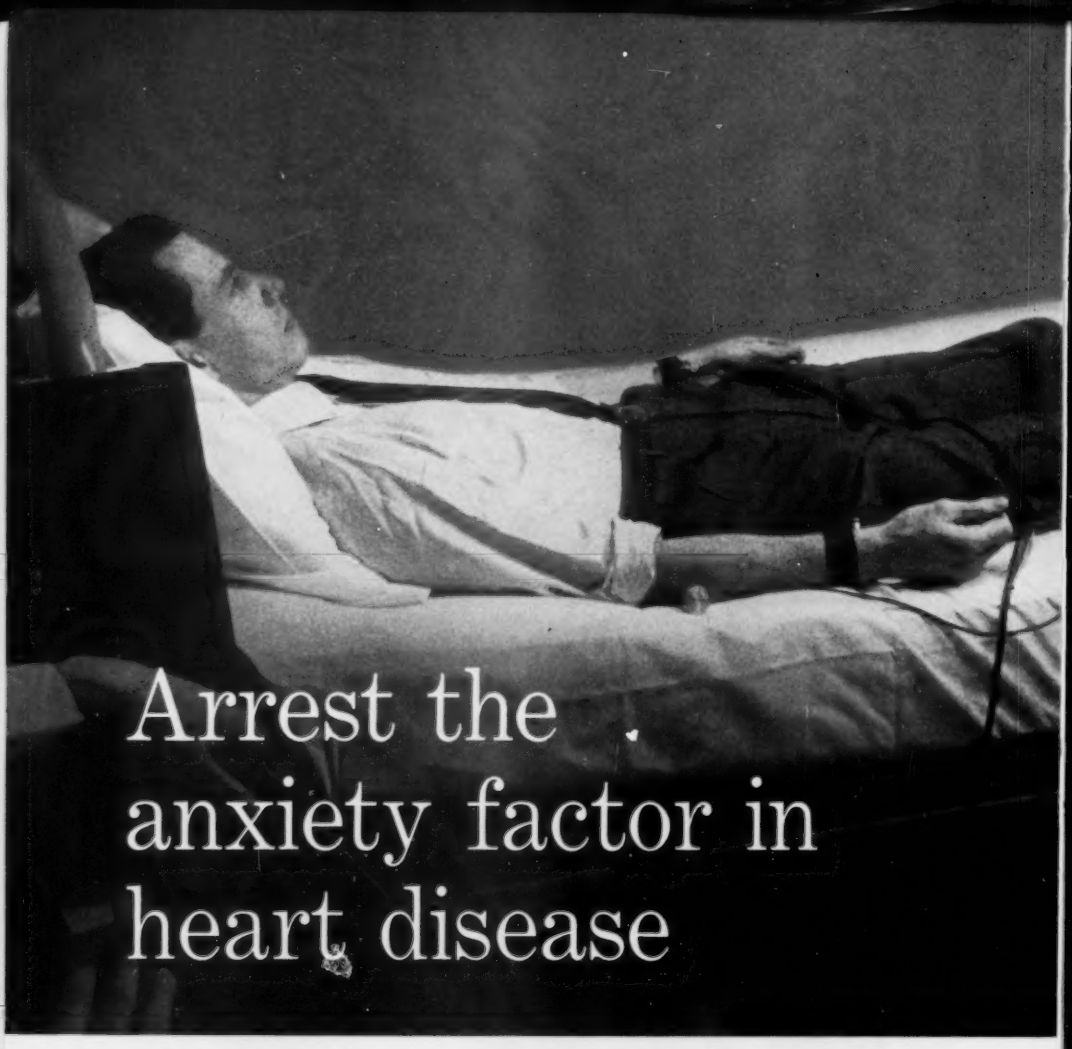

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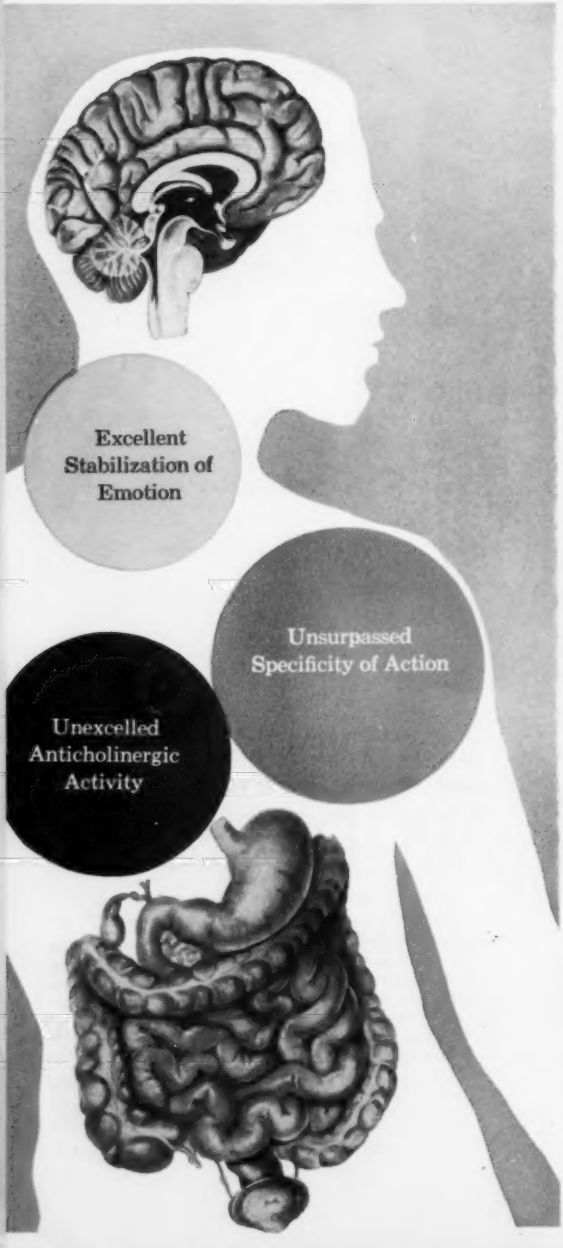

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Postoperative Myocardial Infarction

Report of Thirty-Five Cases

GIORGIO FERUGLIO, M.D.; SAMUEL BELLET, M.D., and HRANT STONE, M.D., Philadelphia

The recent literature concerned with postoperative myocardial infarction is limited to relatively few detailed reports.[1-3] Advances in surgical and anesthetic procedures and the improvement in the pre- and postoperative care of the patient entail revision of the data of the older literature.

Myocardial infarction is not an uncommon postoperative complication; it is particularly prevalent in the older age group. Recent data (1954, 1956)[4,5] suggest that myocardial infarction is responsible for 10% of the deaths following major operations in patients above the age of 60 years. The incidence may be even greater, since necropsies indicate that the clinical diagnosis of myocardial infarction as the cause of sudden death is missed in about 50% of the cases.[5] The purpose of this study is to present three years' experience (1954-1957) at the Graduate Hospital of the University of Pennsylvania with postoperative myocardial infarction and to discuss the predisposing and precipitating factors, clinical findings, early diagnosis, and possible methods of prevention and treatment.

Submitted for publication March 10, 1958.

Research Fellow in Cardiology, Graduate Hospital of the University of Pennsylvania (Dr. Feruglio). Director, Division of Cardiology, Philadelphia General Hospital; Director, Division of Cardiovascular Diseases, Graduate Hospital of the University of Pennsylvania (Dr. Bellet). Associate Professor of Anesthesiology, University of Pennsylvania Graduate School of Medicine; Director of Anesthesiology, Graduate Hospital of the University of Pennsylvania (Dr. Stone).

Material and Method of Study

Thirty-five cases of postoperative myocardial infarction were selected after careful examination of the clinical records of approximately 21,000 patients (0.16%) who were subjected to major and minor surgery in the last three years. Most of these cases were clinically followed by one of us (S. B.). The diagnosis of myocardial infarction was established by clinical and electrocardiographic data. In six cases the diagnosis was confirmed by postmortem examination. Cases with questionable data or with clinical diagnosis not supported by electrocardiographic or autopsy control were excluded from this study. The data in each case were carefully reviewed from the standpoint of preexisting heart disease, type and length of operation, anesthesia, and the development of hypotensive episodes during operative surgery or in the immediate postoperative period.

Findings

Age, Sex, and Preoperative Status.—Twenty-two patients were men and 13 were women. Thirty of these patients were white; four were Negroes, and one was Chinese. They ranged in age from 43 to 83 years, with an average age of 69 (Table 1).

TABLE 1.—*Age Distribution*

Age, Yr.	Cases
40-50	4
50-60	4
60-70	11
70-80	13
80-90	3
Total	35

TABLE 2.—*Types of Cardiovascular Disease*

Hypertensive cardiovascular disease	13
Arteriosclerotic cardiovascular disease	7
Hypertensive and arteriosclerotic cardiovascular disease	8
Coronary arteriosclerosis with coronary insufficiency	8
Syphilitic cardiovascular disease	2
No clinical evidence of cardiovascular disease	5

TABLE 3.—*Types of Surgical Procedures Other Than Major Abdominal Operation*

Major thoracic procedure	2
Transurethral prostatectomy	1
Mastectomy	2
Laryngectomy	1
Mastoidectomy	1
Cataract	2
Iridectomy	1
Corneal transplantations	1

The type of cardiovascular disease as determined during preoperative evaluation is shown in Table 2.

The electrocardiographic diagnosis obtained before surgery in 30 patients of this series was (*a*) within normal limits (7 patients), (*b*) slight myocardial abnormality (10 patients), and moderate to severe grade of myocardial abnormality (13 patients). Electrocardiograms were not obtained in five patients.

Type of Surgery and Anesthesia.—The commonest procedure consisted of major abdominal operations (24 cases). The other types of operation are listed in Table 3.

These operations were performed under the following types of anesthesia: local anesthesia (topical and infiltration), 6 cases; spinal anesthesia with supplementation (tetracaine [Pontocaine] or dibucaine [Nupercaine]), 3 cases, and general anesthesia (thiopental [Pentothal], cyclopropane, ether), 26 cases. The length of the surgical procedures ranged from 20 minutes to 6 hours.

Hypotension.—Twenty-five patients manifested hypotensive episodes of varying length and degree during surgery or in the immediate postoperative period. Fifteen patients developed mild hypotension, with a fall of 30-60 mm. systolic and 10-30 mm. diastolic. Ten patients had a severer fall in the blood pressure, and two of these manifested surgical shock when in the recovery room, with no obtainable systolic pressure for periods of two and three hours, respectively. In 12 patients the hypotensive state required administration

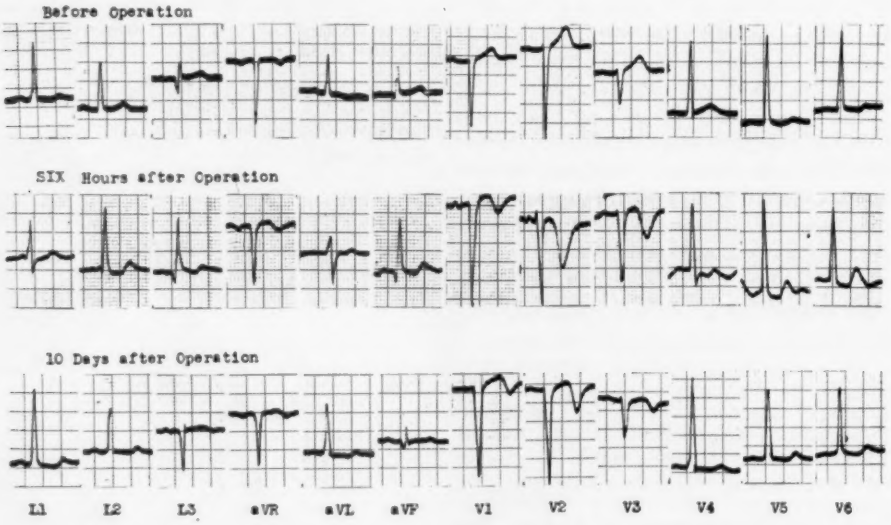

Fig. 1.—A 68-year-old white woman had an intestinal resection on May 13, 1955. Six hours after operation she developed chest pain, hypotension, and an irregular pulse. The above serial tracings show an acute anteroseptal myocardial infarction in evolution.

of phenylephrine (Neo-Synephrine) or other drugs to maintain the blood pressure during the operation or in the immediate postoperative period.

Six patients presented a moderate blood loss and three a blood loss of severe degree, with a drop in hemoglobin which ranged from 5 to 8 gm. %.

Clinical Features of Postoperative Myocardial Infarction.—The clinical features presented by the patients of these series differed in many aspects from the usual type of myocardial infarction. Only 15 patients of this group complained of chest pain, and in only 7 was it severe with a typical radiation to the neck and shoulders. The occurrence of the hypotensive state usually coincided with or was followed by a myocardial infarction in 29 patients. Two of this group were in shock for several hours; two patients developed acute pulmonary edema, and two manifested congestive heart failure.

Seven patients manifested arrhythmias as follows: auricular flutter (one case), auricular fibrillation (one case), and frequent extrasystoles (five cases). Tachycardia, with a rate between 100 and 150 a minute was observed in four cases.

TABLE 4.—*Postoperative Period During Which Infarction Occurred*

Postoperative Day	No. of Cases
Same day	12
First	4
Second	7
Third	3
Fourth	1
Fifth	4
Sixth	4

The postoperative periods during which infarction occurred are shown in Table 4.

The diagnosis of myocardial infarction was made on the operative day in approximately one-third of the group, in one-third within the first three days, and in the remaining third between the fourth and the sixth day of the postoperative period.

Electrocardiographic Findings.—The sites of the myocardial infarction, as determined from the electrocardiogram (29 cases), from the electrocardiogram and necropsy (1 case), and from the autopsy findings (5 additional cases) are summarized in Table 5.

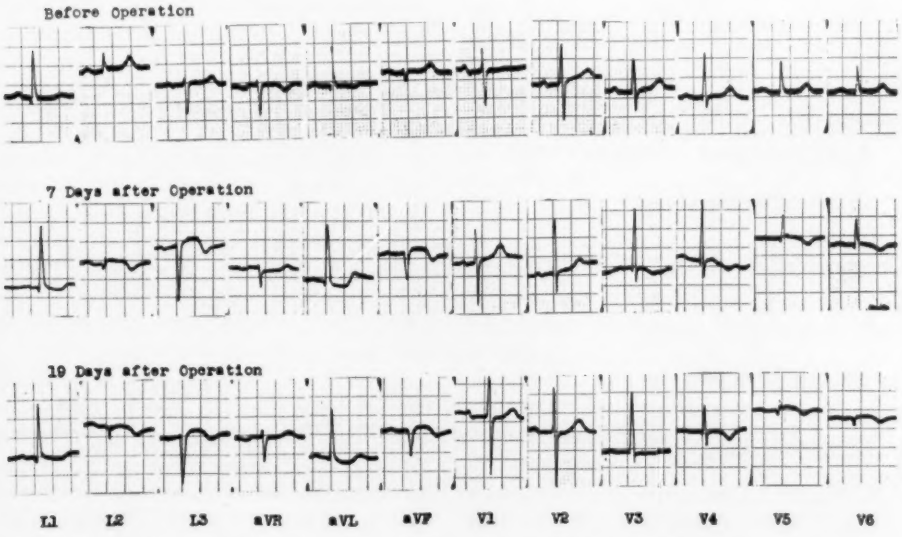

Fig. 2.—An 82-year-old white woman had a simple mastectomy under general anesthesia on Nov. 16, 1956. On the seventh postoperative day she developed sharp pain in her left shoulder and an irregular pulse. The above tracings show the evolution of an acute infero-lateral myocardial infarction.

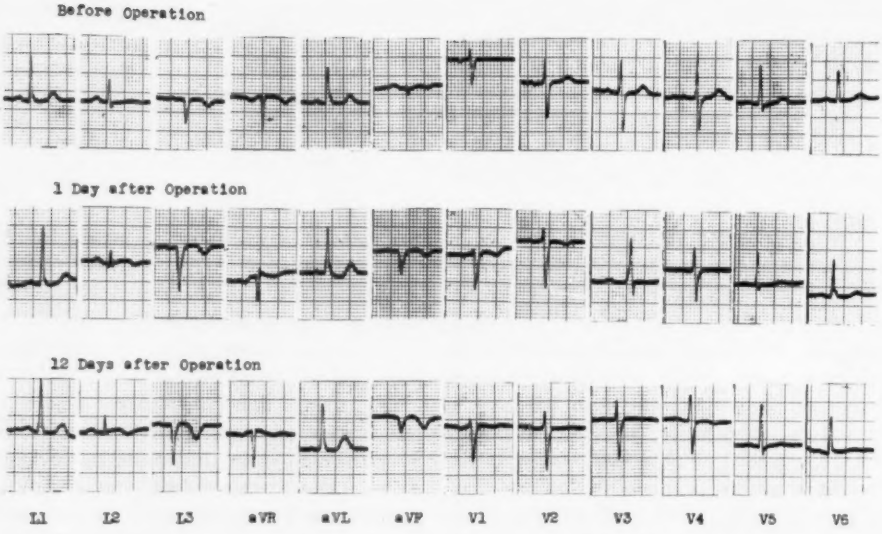

Fig. 3.—An 83-year-old white woman was operated on for cataract on April 2, 1957. One day after operation she developed hypotension and precordial discomfort. The EKG taken at that time shows evidence of an ischemic process affecting the inferior and the anteroseptal wall. Electrocardiographic changes persisted and were still present in the tracing taken 12 days postoperatively.

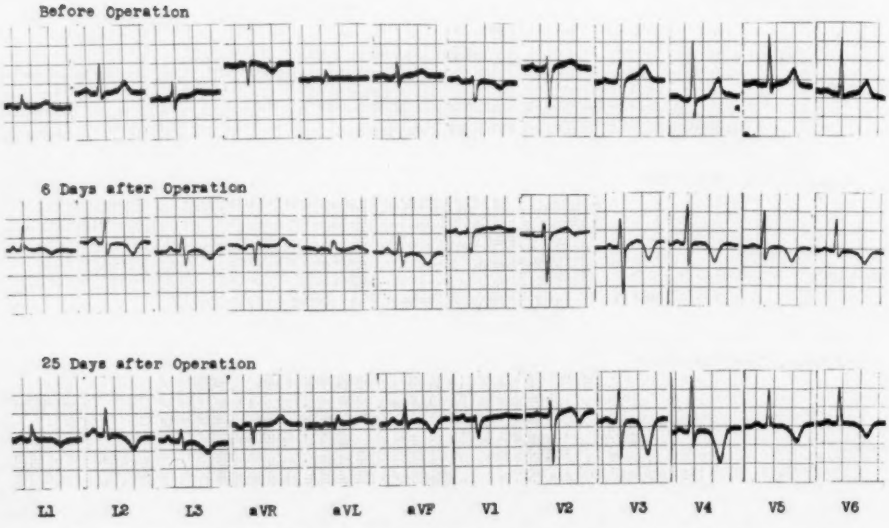

Fig. 4.—A 53-year-old white woman had a cholecystectomy on Jan. 5, 1956. On the fourth postoperative day she developed a hypotensive episode. The following day she complained of a severe substernal pain. The above tracings taken 6 and 25 days after operation, respectively, show evolutionary changes of an acute inferolateral myocardial infarction.

TABLE 5.—*Site of Myocardial Infarction*

	Cases
Anteroseptal	9
Anterior	1
Anterolateral	8
Extensive anterior	1
Inferior	2
Inferolateral	4
Posterior	2
Posterolateral	1
Transseptal	1
Subendocardial	6
Total	35

Clinical Course and Fate.—Eleven patients (31.4%) died within 10 days after the onset of the myocardial infarction. In all these cases death was directly related to this state. Necropsies performed in six of these patients confirmed the clinical diagnosis.

The clinical course in most of the patients who survived was rather mild. Twenty-four patients of our series improved after the usual therapeutic measures and were discharged from the hospital within two to four weeks. Ambulation was postponed for one or two weeks or longer, depending on the patient's clinical state. In six cases the electrocardiogram returned to normal within 10 to 16 days.

Comment

Surgery in the older age group and in patients with preexisting cardiovascular disease, particularly with coronary artery involvement, entails an added risk and the danger of coronary thrombosis. The problem of prevention of these complications is of considerable importance.

Predisposing Factors.—Most important of the predisposing factors was arteriosclerotic heart disease, coronary arteriosclerosis occurring particularly in the older age group. In our series most of our subjects manifested arteriosclerotic and hypertensive heart disease. The existence of or a tendency to develop congestive heart failure was not an important predisposing factor. The presence of polycythemia was an important contributing factor. Emotional disturbance, with the tension, fear, or anxiety accompanying surgery, seems to predispose to the development of myocardial infarction. This may be due to increased blood coagulability.[16] The fact that 78% were over 60 years of age and that the average age of this group was 69 years merits special emphasis.

Precipitating Causes.—There are certain types of patients, as noted above, who are particularly vulnerable to the development of vascular occlusion. Of the factors immediately responsible was the presence or the precipitation of the hypotensive state, particularly if accompanied by shock. The likelihood of the development of a myocardial infarction is increased with prolonged duration of the hypotensive episode. The presence of hemorrhage was an additional complicating factor. These factors result either in an actual occlusion of a major or several small vessels or in the production of a prolonged episode of coronary insufficiency, leading to the formation of areas of necrosis in the heart muscle.[19-21]

Other factors that lead to a relative decrease in coronary blood flow are the development of rapid ectopic rhythms (auricular fibrillation, auricular flutter, paroxysmal auricular tachycardia) and the development of extremely slow heart rates (below 30 per minute) which may accompany a hypotensive state.

Patients in the older age group are often extremely sensitive to the anesthetic agent; this leads to the production of varying degrees of anoxia due to respiratory depression, with subsequent development of respiratory acidosis. All of these are factors in the production of the resultant circulatory depression and the hypotensive state. Curare and other preparations employed to obtain muscular relaxation, by reducing the excursions of the diaphragm and decreasing the function of the abdominal and accessory muscles of respiration, tend to decrease the venous return and may cause or aggravate a state of anoxia. It

should be remembered that circulatory collapse may occasionally be induced by these drugs.[23] In the postoperative period following abdominal operation the splinting of the diaphragm because of pain results in shallow breathing, which decreases the venous return, with the resultant production of or aggravation of a state of potential coronary insufficiency.

Finally, it has been demonstrated that surgical stress, by inducing absorption of the product of tissue injury, and changes in blood components,[30,32,33] volume, and viscosity, results in significant changes in blood coagulability, which are considered, together with circulatory conditions and vascular factors, as the main causes of postoperative thromboembolic complications. In a recent study [43] on postoperative changes in blood coagulation in the older age group, we have observed that, after a transient postoperative state of hypocoagulability, patients over 65 tend to show a definite trend toward hypercoagulability by the seventh postoperative day, which is characterized by an increase in thromboplastin activity, platelet count, and heparin tolerance.

Diagnosis and Differential Diagnosis

Diagnosis of postoperative myocardial infarction presents difficulties in two respects. 1. This diagnosis is often missed because of the underlying clinical state of the patient and the use of analgesic drugs, and because these patients are not studied by frequent routine electrocardiograms. Indeed, only 50% of the postoperative cases with necropsy with myocardial infarction were diagnosed clinically. 2. The diagnosis may be made somewhat more frequently than actually occurs because of the atypical clinical picture and equivocal electrocardiographic changes in some patients.

The possibility of a myocardial infarction should be considered in the postoperative period, particularly in the older patients with preceding heart damage following a hypotensive episode. The presence of pain, fever, leukocytosis, and abnormal serum transaminase levels is usually not of great help in establishing the diagnosis because of the underlying clinical state of the patient and the multiple causes of these manifestations. The electrocardiograms are of two types: (*a*) those of clear-cut transmural infarction, and (*b*) those which show chiefly T-wave changes, consisting usually of deeply inverted variety, which follow evolutionary changes toward normal in the favorable case. It is this latter category that requires careful consideration from the standpoint of differential diagnosis.

Among the conditions which should be considered in the differential diagnosis are the following:

Acute cor pulmonale is frequently difficult to rule out because it is often indistinguishable from the myocardial infarction. In addition, the electrocardiogram may show T-wave inversion because of the associated global ischemia of the heart muscle. The points in favor of acute cor pulmonale are the presence of preceding phlebothrombosis, hemoptysis, development of localized pulmonary signs, and evolutionary changes in serial electrocardiograms. Occasionally acute myocardial infarction and acute cor pulmonale may coexist. This was true in one of our cases. After thoracic operations, particularly those in the proximity of the pericardium, electrocardiographic changes suggestive of acute pericarditis may occur which simulate those of acute myocardial infarction. The two patients of our series with thoracic operations (esophagectomy and hiatal hernia, respectively) manifested changes which were suggestive of coronary occlusion rather than acute pericarditis. Electrolyte alterations, particularly hypokalemia, may in some instances produce T-wave changes which resemble those of myocardial infarction. Serial tracings, however, usually show a prolongation of the Q-T interval, which frequently helps to differentiate from the tracings of acute myocardial infarction. Often, however, the differential diagnosis is impossible without

chemical estimation of electrolytes. In our cases hypokalemia in doubtful cases was ruled out by chemical studies.

The use of certain drugs, particularly digitalis, quinidine, and vasopressor agents, may produce T-wave inversion. The T-wave alterations produced by these agents are generally of a nonspecific type and usually disappear with discontinuance of these drugs. The effect of these drugs in producing electrocardiographic changes was ruled out in all the cases in this series.

Treatment and Prophylaxis

The therapy of postoperative myocardial infarction is similar to that of myocardial infarction unrelated to surgical procedures. However, certain complicating factors are involved. In patients of the older age group, and in the presence of preexisting coronary artery or other thromboembolic disease, unless specific contraindication exists, prophylactic anticoagulants administered from the 3d to the 10th postoperative day may be of help[37,38] in avoiding thromboembolic phenomena. The prophylactic use of plasmin in patients with the anginal syndrome and those who have sustained hypotensive states during surgery or in the immediate postoperative period is now under investigation.

Where the myocardial infarction is of a mild and uncomplicated type, ambulation may be postponed for one or two weeks.

The prevention of postoperative myocardial infarction is one of the important problems in surgery today, particularly in the older patients with preceding heart damage. The measures already employed include optimum preparation of the patient from the standpoint of heart failure, arrhythmias, anemia, electrolyte imbalance, decrease of anxiety, and the performance of the operation with a minimal degree of tissue damage, anoxia, and blood loss. Hypotension should be avoided where possible. When this occurs, early recognition should be made and immediate therapy with vasopressor agents and transfusions instituted, if necessary. The longer the duration of the hypotensive state the greater is the likelihood of the development of myocardial infarction and the greater its extent.

Following operation, attention should be paid to the avoidance of the dehydration, electrolyte imbalance, and anoxia. Routine electrocardiograms should be taken frequently in the postoperative period, particularly in the group where the complication tends to occur.

Prognosis

The mortality of subjects with postoperative myocardial infarction varies within a wide range, from 30% to 66% (1952, 1955, 1951).[1-3] In our series the mortality was 31.4%.

The prognosis in the individual patient depends on many factors: preexisting degree of coronary artery damage, the extent of the infarcted area, and the presence of complicating visceral diseases. In the older age group the prognosis in rather extensive infarcts is poor. It is hoped that early diagnosis and appropriate therapy may be of help in decreasing this mortality.

Summary

The problem of postoperative myocardial infarction has assumed increasing importance because of the increasing frequency of operative procedures in patients with coronary disease, particularly in the older age group. We have recorded our experience relative to the development of postoperative myocardial infarction during a period of three years. During this period 35 patients with this complication were observed, in a series of 21,000 operations. It is of interest that, although this complication was observed more frequently during major operative procedures, it was also observed with minor operations. The clinical picture, the diagnosis, and the differential diagnosis are discussed. The presence of preexisting heart damage, particularly involving the coronary arteries in the older

age group, is an important predisposing factor.

The occurrence of a hypotensive state during operation is an important precipitating factor. The possible prevention and early recognition and treatment of the hypotensive state may be of help in preventing or decreasing the size of the infarcted area.

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Viremia in Human Mumps Virus Infections

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The isolation of mumps virus from the blood of a patient has been reported on but one occasion, in 1949.[1] The lack of subsequent confirmatory reports, then, leaves the question of viremia in mumps somewhat in doubt. The present paper reports three subsequent isolates from the sera of two patients.

Materials and Methods

Virus Isolation.—Serum and spinal fluid to be tested for the presence of virus were injected undiluted into the amniotic sac of 7-day-old embryonated eggs. Each egg received 0.2 ml. of inoculum. Eggs were incubated for six days at 37 C and then chilled overnight at 4 C. The eggs were then opened and the allantoic and amniotic fluids removed separately. The fluids from each egg were then tested for the presence of a hemagglutinin by addition of 0.5% chicken red blood cells. When no virus was obtained on primary passage, two blind passages were made with pooled amniotic fluids. If negative fluids were still obtained at third blind passage, further egg passages were discontinued.

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Saliva to be tested for virus was incubated with equal volumes of saline containing 2000 units of penicillin and 2000μg. of streptomycin at 37 C for 30 minutes. This was then centrifuged at 4000 rpm for 30 minutes and the upper two-thirds of the supernate removed and used as egg inoculum.

Virus Identification.—The first two mumps virus isolates in these studies represented the first time that mumps virus had been recovered or worked with in this laboratory. Subsequent to the recovery of these isolates, mumps virus was obtained from Lederle Laboratories as an allantoic-adapted strain. This was used as antigen to identify mumps antibody in various human sera. These sera, called "mumps antisera," became our serologic reference, and new viral isolates were tested against the reference serum for viral identification. In all serologic studies the hemagglutination-inhibition test was used, as described previously.[2]

Results

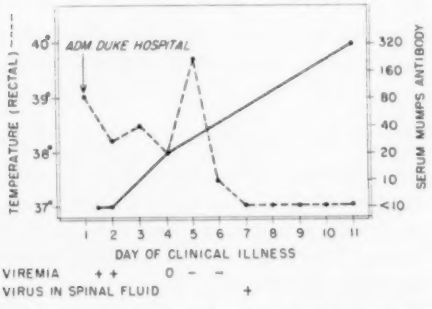
Of 15 patients listed in the accompanying Table who had mumps infection proved serologically, virus was isolated from the blood of 2. Mumps virus was isolated from the serum of Patient 1 on two specimens taken about 12 hours apart, but a subsequent serum specimen taken from the same

Virus Studies on Fifteen Cases of Mumps

Patient	Diagnosis	Virus Isolations			Antibody Titer at Time of Virus Isolation	Subsequent Antibody Titer
		Blood	Saliva	Spinal Fluid		
1	Encephalitis	+	+	+	<10 *	320 *
2	Encephalitis	0	—	+	40	640
3	Encephalitis	0	—	+	40	640
4	Encephalitis	0	—	+	80	320
5	Encephalitis	—	—	+	20	160
6	Parotitis	+	+	—	<10	320
7	Parotitis	0	+	—	20	640
8	Parotitis	0	+	—	20	160
9	Parotitis	0	+	—	40	160
10	Parotitis	0	0	—	40	320
11	Parotitis	0	0	—	20	1280
12	Parotitis	0	0	—	40	640
13	Parotitis	0	0	—	80	320
14	Parotitis	0	—	—	40	320
15	Parotitis	0	—	—	40	320

* Reciprocal of serum dilution.

patient was negative (Figure). A spinal fluid specimen taken five days later, however, was positive for mumps virus. The third isolate was from Patient 6. Serum at the time of virus isolation contained no demonstrable antibody. A second serum specimen, taken three days later, contained no virus, and the antibody titer at this time was 1:20. Virus was also isolated from this patient's saliva; however, spinal fluid was not obtained for virus studies. Virus was recovered from the two positive serum specimens from Patient 1 on first egg passage. The third isolate from Patient 6 was recovered on third passage.



Relation of mumps viremia to clinical disease and antibody response in Patient 1.

No attempts were made to isolate virus from serum until after infections were identified as mumps by a fourfold or greater rise in mumps serum antibody as measured by the hemagglutination-inhibition test. No special treatment of the blood was done: It was allowed to clot; the sera separated in the usual manner and stored at −70 C in glass sealed ampules. Spinal fluid and saliva were tested for presence of virus without storage of these materials.

It should be noted that in serum specimen 1 from Patient 1 residual red cells present before the serum was centrifuged settled into a typical viral hemagglutination pattern. This observation, in fact, provided the impetus for the present studies. After virus was shown to be present in this sample, it was titered in an attempt to quantitate the amount of virus. A single titration in eggs revealed virus in less than a titer of $10^{1.0}$ median egg-infectious doses. This serum was tested for the presence of cold agglutinins after storage for two weeks at −70 C, and none was present. It is presumed that the initial agglutination seen was due to virus, but this was not established definitely.

Comment

The various complications which may follow mumps parotitis, such as meningoencephalitis and orchitis, would suggest that the virus is widely disseminated throughout the body; yet viremia in this disease has been reported by but one investigator. Virus is easily recovered from the spinal fluids and has recently been demonstrated in the urine.[3] In view of these findings, it would appear logical that the virus is transported to these sites via the blood; yet such isolates are obviously rare. It would appear that isolation of virus from the serum in the presence of serum antibody would not be feasible, and, indeed, all isolates herein reported were made prior to the onset of demonstrable mumps serum antibody. Unfortunately, such patients are difficult to obtain. In fact, of more than 100 mumps patients' sera tested by me, only three acute-phase sera have not shown antibody. Despite the apparent logic of the above, Kilham's isolate was made in the presence of a low (1:16) but definite antibody titer. Thus, the factors which contribute to the general lack of success in demonstrating mumps viremia are, as yet, unknown.

Summary

Mumps virus has been demonstrated in the serum of two patients early in the course of clinical mumps virus infections at a time when serum antibody to mumps virus had not yet appeared.

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Myxedema, Pseudomyotonia, and Myotonia Congenita

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For the student of neuromuscular disorders, the thyroid gland poses several unsolved problems. Thus, hyperthyroidism has been shown to be associated with myopathy and ophthalmoplegia and may be related in some manner to myasthenia gravis and periodic paralysis.[1] Similarly, the concurrence of hypothyroidism and muscle dysfunction has been noted repeatedly.[2] Again, certain questions have arisen concerning the part played by thyroid hypofunction in myotonia. Five principal types of association are at issue.

A majority of patients with evident myxedema will show a delay in the relaxation of muscle after deep tendon reflexes are elicited. The phenomenon has been termed *pseudomyotonia*. Lambert[3] demonstrated that the delay includes all phases of the tendon reflex, but only the slowing of relaxation is obvious clinically. Hormone replacement sufficient to correct the basal metabolic rate and the clinical signs of myxedema eradicates the pseudomyotonia. While the nature of the disturbance in muscle function is not explained, the etiologic relation to hypothyroidism is clear. The phenomenon is noted here in order to differentiate it from those which follow.

Myotonic dystrophy has attracted the attention of endocrinologists because of the gonadal deterioration, alopecia, and cataracts which comprise so prominent a part of the syndrome. In some series of cases, thyroid disease has been observed with more than the expected frequency. Usually the lesion has been only nontoxic goiter,[4] but occasionally borderline hypothyroidism has been suggested. Scarcely ever has an author noted significant improvement in the myotonia as the result of thyroid or antithyroid therapy or after thyroidectomy.[5] Although the somewhat unexpected incidence of thyroid disorder in this disease is not explained, no satisfactory evidence of an etiologic relation in either direction has been adduced.

The designation *Hoffman's syndrome* has been given to cases of myxedema in which there is hypertrophy and stiffness of muscles and difficulty in relaxing them after contraction. The original patient[6] demonstrated what was taken to be true myotonia in response to percussion and electrical stimulation as well as in active movement. All of these signs were more marked in winter. There was no family history of a similar disorder. The disability accompanied myxedema subsequent to thyroidectomy for nontoxic goiter, and it was partly relieved by thyroid replacement therapy. It differed from that of Thomsen's disease in that stiffness and sluggishness remained after exercise. Whether the slowing of contraction should be considered identical with pseudomyotonia is not clear; that it is not true myotonia was shown by Thomasen[7] when he demonstrated the absence of the repetitive electric discharges characteristic of that state.

Hypertrophy or pseudohypertrophy of muscle in myxedematous children has been called *Debré-Sémelaigne's syndrome*.[8] The weak muscles are described as "hard" or "hypertonic," and this would seem to be the

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source of confusion with myotonia. True myotonia apparently has not been described in these patients. In some cases the muscular disorder has been overcome by effective treatment of the myxedema.

Finally, occasional instances have been reported of a condition clinically identical with *myotonia congenita* appearing in association with myxedema.[9] These have been patients with negative family histories and no previous muscular complaints who developed widespread myotonia as a result of disease or surgical ablation of the thyroid gland. Interest is aroused by the fact that their complaints have apparently yielded completely to thyroid therapy, while in classical Thomsen's disease thyroid hormones produce no amelioration of symptoms.[7] In the present case study, an apparently similar association between myxedema and true myotonia was explored.

Report of a Case

A 39-year-old white housewife came to the clinic in November, 1954, in the eighth month of her eighth pregnancy, for prenatal care. She gave a history of goiter since the age of 15, intermittently treated with iodine. Neither thyrotoxicosis nor hypothyroidism was suggested by the history, but, during her sixth pregnancy, nine years before, she had complained of "strangling" sensations, apparently related to growth in size of the gland. Symptoms subsided on treatment with strong iodine (Lugol's) solution. A note was made of "difficulty in going up stairs" and of "rheumatism" in the fingers, but these were mild complaints. There were no concomitant findings, and no special attention was paid to the muscles. In December, 1954, the patient was delivered of a normal girl. During postpartum clinic visits, the patient complained of increasing size of her goiter, and in April, 1955, she was sent to the diagnostic clinic for study.

Here she complained of the appearance of a nodule in the cervical mass and of slight neck tenderness and difficulty in swallowing. An exhaustive student history now elicited complaints of "trouble going up stairs" because of "heavy legs" for about eight years, mild transient "stiffness" of the hands which lessened after use, and occasional paresthesias of the hands and feet in the mornings. *Family history was completely negative for similar or related complaints.* A 2×2 cm. nodule was noted in the upper pole of the right lobe of a diffusely enlarged thyroid gland. There was hyperpigmentation of the palmar skin, particularly in the creases. Clinically the patient seemed euthyroid. Protein-bound iodine was 5.3μg. per 100 ml.; I^{131} uptake was 63%, excretion 25%; cholesterol was 225 mg. per 100 ml.

In May, 1955, she was admitted for thyroidectomy. A more detailed history now produced the information that she could not step up onto a chair without help and that, if she bent over at the waist, she required the help of her arms to straighten up. No mention was made of neuromuscular abnormality, and it was specifically stated that "the grip is normal."

On May 18 subtotal thyroidectomy was performed. The gland contained many nodules, which were noted to be benign on microscopic examination. An estimated 3 gm. of the right lobe was left in situ, and the remainder of the gland was removed. No parathyroid tissue was identified at operation or in the surgical specimen. Ten hours after completion of the operation, the patient complained of numbness and tingling of the extremities and carpopedal spasm developed. Chvostek's sign was positive. Intravenous calcium gluconate produced some but not dramatic relief. Repeated episodes of tetany occurred during the next few days, and at these times serum calcium varied from 8.3 to 9.2 mg. per 100 ml.; total protein was 8.0 gm. per 100 ml.; albumin, 5.5 gm. per 100 ml., and phosphorus varied from 5.1 to 5.5 mg. per 100 ml. Response to intravenous calcium salts was satisfactory. In spite of the relatively high serum calcium values, probably accounted for by the elevated protein values, it seemed evident that the tetany resulted from hypoparathyroidism. The patient was discharged asymptomatic on May 28 and was advised to take vitamin D, 100,000 units, and calcium gluconate, 15.0 gm., by mouth daily.

On July 6, 1955, the patient was admitted for dilatation and curettage because of irregular bleeding. "Secretory endometrium and chronic cervicitis" was the diagnosis. During this admission it was noted that "grip is weak in both hands, and patient shows myotonic type of slow relaxation," but no other muscular or neurologic signs or symptoms were discovered. A complaint of "spasms of all muscle groups, particularly on first starting to use them" was assumed to be the result of tetany, since Trousseau's sign was positive. She returned to the metabolic clinic on July 18.

Complaints at this time included numbness and tingling of the extremities and face and a "frozen" feeling in the legs, consisting of difficulty in using the muscles until several contractions had been made. She was noted for the first time to appear "dull" and to talk "slowly and carefully." Chvostek

Fig. 1.—*A*, the patient, on July 30, 1955, at the height of her myxedema. Note dry skin, puffy eyelids, lateral thinning of eyebrows, and languid expression. The right border of the tongue has been percussed with a reflex hammer and exhibits a notch which persisted almost a minute. *B*, the patient, on Nov. 5, 1955, after thyroid therapy.

and Trousseau signs were present. There were periorbital puffiness (Fig. 1*A*), and the muscle relaxed slowly after elicitation of the Achilles reflex. "Stiffness" of the muscles was noticeable particularly in her difficulty in relaxing her hand grip. These findings prompted readmission to the hospital (July 26 to Sept. 2, 1955).

New complaints included slowing of movements, dryness of the skin, and decreased tolerance to cold. On numerous occasions she was unable to release an object grasped in the hand. Once again *persistent questioning brought out no evidence of relevant complaints in others members of the family.* Physical findings now included the following: blood pressure, 100/70; pulse, 60. The general appearance was "pasty and pale," with puffy eyelids. All movements were slow, and speech was described as "thick." The skin was doughy, rough, and dry. The thyroidectomy cicatrix was unremarkable. Chvostek and Trousseau signs were absent, but the muscles relaxed extremely slowly when tendon reflexes were elicited. Grasp myotonia was marked, gradually disappearing on successive voluntary contractions. Percussion of various muscles produced deep furrows which persisted for as long as 40 seconds, sometimes accompanied by fascicular twitching. When the tongue was rapped sharply against a wooden tongue depressor with a reflex hammer a deep notch appeared which remained for several seconds (Fig. 1*A*). Laboratory findings: volume of packed red cells, 37%; calcium, 10 mg. per 100 ml.; phosphorus, 5.3 mg. per 100 ml.; cholesterol, 390 mg. per 100 ml.; protein-bound iodine, 3.4μg. per 100 ml.; I^{131} uptake, 3.8%; I^{131} excretion, 67%. An electrocardiogram showed a rate of 63; normal rhythm; P-R interval, 0.21; QRS, 0.08; QT, 0.39; P waves, broad and flat, and T waves, low. The tracing was termed "consistent with myxedema heart."

At this point the diagnosis of myxedema appeared unequivocal. The patient was therefore included in a series of persons with hypothyroidism whose muscle function was being investigated by electrical methods. To this date, eight patients had been studied. They had all displayed characteristic clinical and chemical stigmata of myxedema. They were of both sexes and ranged in age from 10 to 73 years. In some, myxedema had appeared spontaneously, while others had deficient thyroid function following Hashimoto's struma, I^{131} irradiation for carcinoma of the gland, or thyroidectomy for nontoxic goiter. In all the deep tendon reflexes displayed the markedly slow relaxation defined above as pseudomyotonia. None, however, had complaints of stiffness or difficulty in relaxation, and none demonstrated the prolonged contrac-

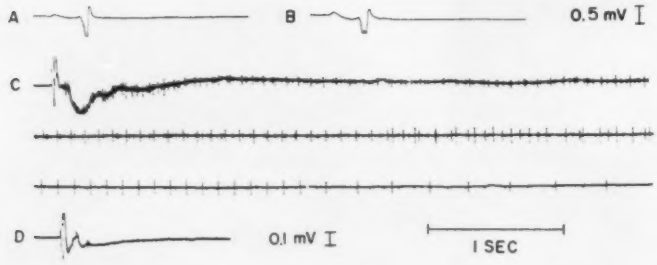

Fig. 2.—Electromyograms of biceps reflex. Bipolar needle electrodes. *A* and *B*, pseudomyotonia in a case of spontaneous myxedema. First and fifth taps. *C* and *D*, on Aug. 2, 1955, before therapy. First and fifth taps.

tion on direct muscle percussion or the "warm-up" after exercise characteristic of true myotonia. An electromyogram typical of this group of patients is reproduced in Figure 2 (*A* and *B*). Paired needle electrodes, insulated except at their tips, were inserted into the belly of the left biceps brachii. Sharp, vigorous blows to the tendon by means of a reflex hammer produced the potentials shown. After the reflex jerk, the tracing returned rapidly to the baseline. No electrical discharge accompanied the slow relaxation of the muscle. The fifth tap produced a potential of essentially the same duration as the first. Despite the striking clinical appearance of pseudomyotonia, the electrical records could not be differentiated from normal ones.

To these findings, the patient presented a marked contrast. Ten weeks after her thyroidectomy, the first electrical recordings were made (Fig. 2, *C* and *D*). Voluntary contraction, tendon taps, and immediate muscle percussion all produced the characteristic electromyogram of true myotonia. The initial action potentials accompanying contraction were grossly normal, but the markedly prolonged relaxation phase showed the impressive decrescendo activity classically associated with Thomsen's disease. Moreover, as in myotonia congenita, "warm-up" occurred on successive excitations and the records concomitantly assumed a more normal appearance. Because this patient's course had been complicated by tetany of hypoparathyroidism, it was thought prudent to exclude possible effects of hypocalcemia on the electromyogram. At the time of the study, the serum calcium was normal, although the phosphate was slightly elevated (5 mg. per 100 ml.). Rapid intravenous administration of 1.0 gm. of calcium gluconate during the recording produced no apparent change in electrical activity.

On Aug. 9, three months after thyroidectomy, therapy with triiodothyronine was instituted, 50μg. daily orally. This dose was increased to 50μg. three times a day on Aug. 17 and continued at this level until Sept. 23, when medication was changed to desiccated thyroid, 64 mg. twice a day. On Aug. 10 the complaint of difficulty climbing stairs had disappeared. On Aug. 11 it was noted that speech was becoming more rapid and that the facial contour was changing, but percussion myotonia was still weakly present, and relaxation of reflexes was still noticeably slow. By Aug. 26 the face appeared normal (Fig. 1*B*), pseudomyotonia was less pronounced, and percussion myotonia could not be elicited. The patient was discharged Sept. 2. Frequent follow-up visits over the next 26 months disclosed no clinical or chemical evidence of hypothyroidism, although tetany was not always well controlled. Previous symptoms of muscle fatigue and weakness never recurred. Slight difficulty in relaxing the hand grasp occurred unpredictably on occasional mornings. Pseudomyotonia was never again elicited, but minimal percussion myotonia re-

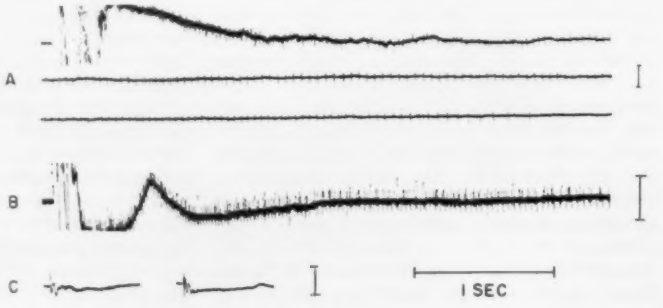

Fig. 3.—Electromyograms of the patient after thyroid therapy. *A*, right radial periosteal reflex on Nov. 5, 1955. *B*, same reflex on Dec. 6, 1955. *C*, right biceps reflex, first and fifth taps, on April 2, 1956. There are still a few late repetitive potentials, but "warm-up" is virtually complete in the second record. Calibrations: 0.2 mv.

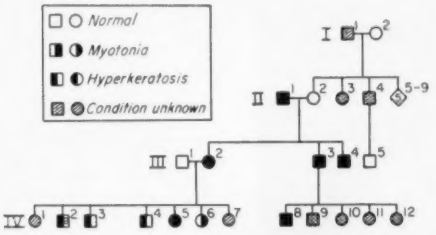

Fig. 4.—Pedigree chart. Note the direct transmission of myotonia and hyperkeratosis to the succeeding generation.

mained. Hospitalization for hysterectomy was uneventful, and again on this occasion *family history of any muscular symptoms was negative.*

On six separate occasions since the patient returned to a euthyroid state, electromyographic studies have been repeated (Fig. 3). Three months after the institution of thyroid therapy, at a time when clinical examination produced only equivocal signs of myotonia, the electrical record was still grossly abnormal (Fig. 3*B*). Examination was repeated April 2 and Nov. 9, 1957. On both occasions the patient was asymptomatic, although she reported that slow relaxation of grasp occurred rarely in the morning. Signs of myotonia were so slight that the examiner believed they would have been overlooked had not the previous history been known. Electromyograms (Fig. 3*C*), showed a few repetitive potentials during relaxation, and warm-up was very rapid. Attempts to increase either clinical or electrical signs of myotonia by chilling with ice and ethyl chloride spray were unsuccessful.

An interesting side-light on the errors of history taking appeared during this last examination. After three years of steadfastly denying symptoms of myotonia, the patient now stated that her slight morning difficulty in relaxing her grip was "no more than when I was a girl!"

The similarity between the electromyograms of this patient and those of classical Thomsen's disease stimulated detailed investigation of the family (Fig. 4 and Table). Since the maternal grandmother (Fig. 4, I-2), was reported to have "stiffness" in hand movements, observations were made of muscle function in her, the patient's mother (II-2), and a maternal cousin (III-5). All was clinically and electrically negative, the noted "stiffness" having been the result of osteoarthritis. The patient's father was dead, and other members of the paternal line were not available.

Two brothers (III-3 and III-4) were so similar that one description will suffice for both. Both were impressively well-muscled persons who denied any relevant symptoms at first encounter. As the family story unfolded, however, each remembered occasional difficulty in relaxing, but both reported they were unimpressed with these very minor symptoms, *since their father had also been similarly affected.* In both brothers, percussion of the tongue or the deltoid muscle (Fig. 5) produced deep grooves lasting the better part of a minute. Myotonia and "warm-up" were easily elicited by grasp or by percussion of the thenar eminence or biceps brachii. Electromyograms showed the characteristic myontonic abnormality (Fig. 6). In the case of one brother (III-4), opportunities arose for repeated examination. Marked fluctuation in the clinical severity of his myotonia occurred, but electrical records varied little. He believed that his difficulty was worse in the cold, but this could not be quantitated objectively. He subsequently died at the age of 36 years, of myocardial infarc-

Data on the Family

Subject	Sex	Age (1955)	Myotonia			Hyperkeratosis		Comment
			Physical Examination	Electromyogram	History	Physical Examination	History	
I-2	F	79	—	—	—	—	—	
II-1	M	--			+		+	Died age 49 "heart attack"
II-2	F	59	—	—	—	—	—	
III-1	M		—		—	—	—	
III-2	F	30	+	+	?	+	+	Propositus
III-3	M	37	+	+	+	+	+	
III-4	M	34	+	+	+	+	+	
III-5	M	31	—	—	—	—	—	
IV-1	F	--						Died age 1 mo. "pneumonia"
IV-3	M	17	—	—	—	+	+	
IV-4	M	11	—	—	—	+	+	
IV-5	F	9	+	+	—	+	+	
IV-6	F	6	+	—	—	—	—	
IV-7	F	8/12						Not examined
IV-8	M	16	+			+	+	

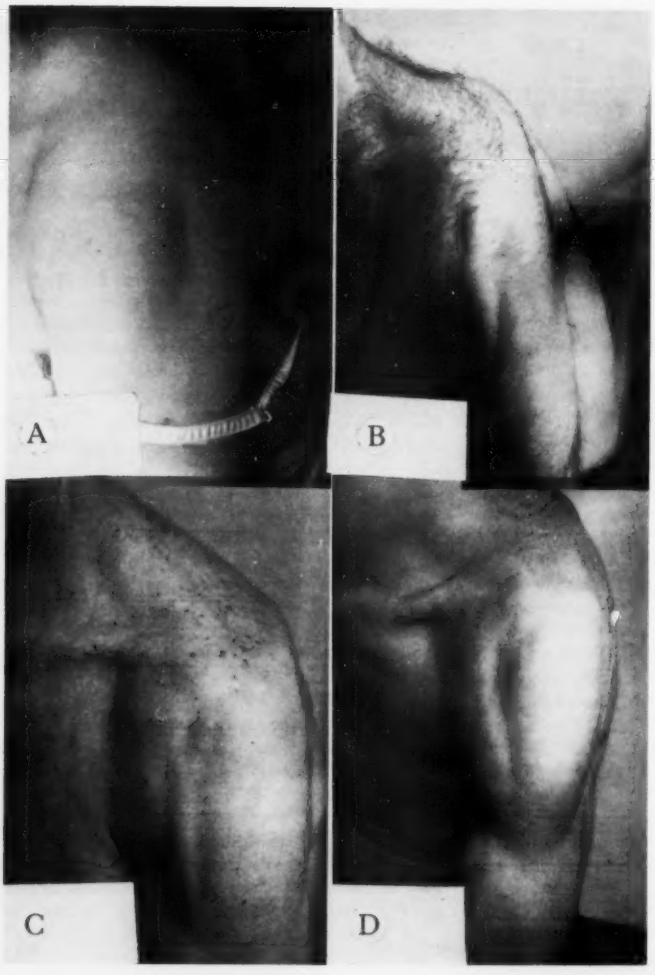

Fig. 5.—*A*, left arm of the patient (July 30, 1955), her brothers (*B* and *C*), and her nephew (*D*). The deltoid muscles have been percussed with a reflex hammer, and persistent deep grooves are apparent.

tion. The cardiac muscle was not abnormal, with the exception of the effects of arteriosclerosis. Sections of skeletal muscle revealed occasional hypertrophic fibers, but this was not deemed sufficient to warrant a pathologic diagnosis.

Investigation of members of the next generation has been incomplete. In only one has myotonia been established beyond doubt by electrical means. This is IV-5, a daughter of the patient. When first seen, at the age of 9 years, this girl and her 6-year-old sister (IV-6) both showed suggestive clinical signs, but no electrical abnormality was elicited. When last seen, at the age of 11 years IV-5 demonstrated a minimal degree of repetitive firing, similar to that illustrated in Figure 3*C*. At the age of 8 years, the electromyogram of IV-6 was still normal. IV-8 resembles his father and uncle in his impressive muscular development, and percussion of his deltoid muscle produces a similar deep, long-lasting groove (Fig. 5), but electromyographic studies were not permitted. IV-3 was clinically and electrically normal.

Among the stigmata of myxedema displayed by the patient, roughness and dryness of the skin were noted. With her return to a euthyroid state, the skin regained its former softness, but her palms and soles remained thickened, dry, fissured. A consulting dermatologist made the diagnosis of *hyperkeratosis palmaris et plantaris* and noted the same condition in the patient's brother (III-4). Other members of the family with unequivocal evidence of this disorder were the other brother (III-3, Fig. 7) and five children in the fourth generation. The patient and both her brothers

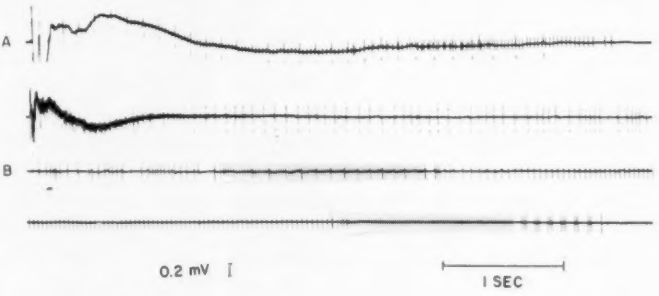

Fig. 6.—Electromyograms of patient's brothers. Immediate percussion of right deltoid. *A*, brother III-3. *B*, brother III-4.

remembered that their father had greased his hands regularly to prevent cracking. No evidence of hyperkeratosis appeared in the maternal relatives of the patient.

Comment.—In this patient, the diagnosis of myxedema was unequivocal. Her symptoms appeared well within the time range regarded as typical of postoperative hypothyroidism,[10] the signs displayed were classical, and laboratory confirmation was definite. Finally, she responded completely to specific therapy. The tetany was established to be the result of hypoparathyroidism. It has been moderately well controlled by vitamin D and calcium therapy.

General Comment

The phenomenon we have termed "pseudomyotonia" is now well known, but its cause remains uncertain. It appears to result from a disorder of the contractile mechanism,[3] perhaps related to abnormal muscle viscosity.[11] The present report confirms the observation of Lambert et al.[3] that the delayed relaxation of tendon reflexes in myxedematous patients is not ac-

Fig. 7.—Hyperkeratosis palmaris et plantaris in the brother, III-3. The thickened dry cracked skin is best seen on the hands. A recent deep fissure is concealed by the bandage.

companied by any demonstrable electrical abnormality. In our experience, pseudomyotonia occurs frequently enough in myxedema of whatever etiology to be considered a usual part of the clinical syndrome. True myotonia differs from this picture in several important essentials.

1. Pseudomyotonia is asymptomatic, apart from the general sluggishness often noted by myxedematous patients, while myotonia is not. Starting with Thomsen's original description,[12] numerous authors have described cases in which the disability constituted a major incapacitation. On the other hand, in the family reported here the three affected adults eventually related minor instances of hindered muscular performance, but the degree of disability was small.

2. The three men pictured in Figure 5 displayed striking muscular development, a feature usually present in myotonia congenita [7] and presumably irrelevant in myxedema. This observation is particularly noteworthy, since in all three the degree of myotonia fluctuated but was never more than mild. The large size of the muscles could, therefore, scarcely be attributed to work hypertrophy.

3. Dimpling of the tongue and deep grooving of the other muscles, persisting for the larger part of a minute after direct percussion (Figs. 1 and 5), was not seen in pseudomyotonia.

4. Thomsen noted in himself and other afflicted members of his family that, with muscular exercise, the defect in relaxation gradually improved.[12] This waning of myotonia has since been called "warm-up." It does not occur in pseudomyotonia, in which condition the reflexes are just as slow after repeated elicitation as after the first tap. In very severe cases of myotonia congenita, "warm-up" may be incomplete, even after considerable exercise. Conversely, patients such as ours, in whom the complaint is mild, may show myotonia only after a rest period.[7]

5. Once again, Thomsen was the first to note the increase of myotonic symptoms under emotional stress and in the cold. In the present family, the history suggested some effect of emotions and chilling, but objective confirmation was lacking. Myotonia certainly fluctuated in intensity, but the responsible stimuli were not identified. Pseudomyotonia apparently varies only with the degree of hypothyroidism.

6. Definitive differentiation between the two conditions is most clearly achieved by electromyography. As noted above and demonstrated in Fig. 2*A* and *B*, pseudomyotonic records are indistinguishable from normal ones.[3] In contrast, myotonia presents an electrical appearance so distinctive as to be quite unlike any other neuromuscular phenomenon (Figs. 2*C* and *D*, 3, and 6). A tendon tap, direct percussion, or voluntary activation is accompanied by apparently normal potentials. During relaxation, however, instead of the normal abrupt cessation of activity, there occurs a positive barrage of firing. Initially repeating at high frequency, these potentials gradually slow down, often to be replaced by the extremely regular discharge of a single unit. Upon a record of this sort there may be superimposed further outbursts of high-frequency discharge, these often showing gradually decrementing amplitude (Fig. 6*B*). The late outburst may not subside for more than a minute. Characteristics of the potentials suggest that they represent firing of single fibers as well as motor units [13] and that among the latter differential fatiguing of some end-plates occurs. The responsible mechanism is still obscure.

In all the above respects, the patient displayed clear evidence of myotonia. With the exception of a few rather dubious cases of so-called "myotonia acquisita," [7] most reported instances of myotonia have been hereditary. The two principal diseases in which the phenomenon is seen are myotonia congenita (Thomsen's disease) and myotonia dystrophica. Paramyotonia, a hereditary disorder in which the muscular complaint occurs only in the cold, is very similar to Thomsen's disease but is geneti-

cally distinct. In our family, objective evidence of the effect of lowered temperature was lacking. Absent also were the classical stigmata of myotonic dystrophy: muscle wasting, frontal baldness, lenticular opacities, and gonadal atrophy. The pattern of inheritance of myotonia present in the family reported here is compatible with that of a dominant trait, the usual finding in Thomsen's disease.[7] It is, therefore, concluded that this family is affected by myotonia congenita and that in the patient the disease is very mild but was temporarily aggravated by myxedema. A similar case has recently been reported by Wade.[14] In his case, however, the myotonia was much severer and the relief afforded by treatment of the myxedema appears to have been less pronounced. He believed the association to have been fortuitous. However, in our patient, the relation of the two diseases was so intimate that the myotonia was clinically inapparent until myxedema supervened. No adequate explanation of this relation is available.

Under a variety of synonyms hyperkeratosis palmaris et plantaris has long been recognized as a hereditary disorder.[15,16] A standard textbook of dermatology[17] describes diffuse and symmetrical thickening of the palms and soles with yellow-brown horny material, in which deep painful fissures occur. The condition is usually apparent at an early age, and in most reported families the mode of inheritance is dominant. We have found no previous reports of its occurrence in association with myotonia congenita. In the present family, all four electrically proved patients with myotonia had hyperkeratosis also. Hyperkeratosis was also definitely present in one child in whom myotonia was unproved and in two in whom electrical examination was negative. It should be noted that the skin disorder is readily identified by inspection, whereas myotonia may be difficult to elicit and may not reach full expression at an early age. There is thus a considerable possibility that, in this family, the diseases always occur together, constituting an example of genetic linkage. However, because of the limited number of examinations of adults in whom the electromyographic findings can be considered definitive, final proof of such linkage is not available.

Attempts to prove consanguinity in the ancestors of this family have been unsuccessful. Since the father of the patient came from a Wisconsin family while the maternal line had been in Utah for several generations, recent consanguinity appears to be unlikely.

In a study of this sort, the importance of accurate genetic information is obvious. A word of caution is therefore in order. Too often the routine statement, "family history was negative," is based upon a casual question tagged onto the end of an otherwise careful history. In the present investigation, the standard history was taken at least 15 times by as many observers and was persistently unrewarding. It has been our experience that patients are often unaware of the complaints of close relatives. When they know such complaints exist, they often fail to associate them with similar difficulties of their own, probably because of a reluctance to admit the possibility of hereditary disorder. If the disease in question is obvious, the more disabling it is the more it is likely to be denied. Thomsen recognized the tendency to avoid the implications of hereditary defect in his own family,[12] and in myotonic dystrophy denial of disability is commonly encountered.[7] In many similar situations the taking of a family history does not obviate the necessity for examination of relatives.

Summary

A 39-year-old housewife developed hypoparathyroid tetany promptly and myxedema two months after thyroidectomy. Simultaneously with the myxedema, symptoms and signs of generalized myotonia appeared, and the diagnosis was confirmed by electromyography. The disorder is differentiated from pseudomyotonia, a common

feature of myxedema, and from other muscular affections occasionally seen in hypothyroid patients.

Unequivocal myotonia was identified in three blood relatives and was probably present in at least three others, none of whom displayed symptoms or signs of thyroid dysfunction. In the patient, myotonia was greatly ameliorated but not obliterated by hormonal therapy sufficient to relieve the myxedema. It is concluded that the family is affected by myotonia congenita and that in the patient the disorder was too mild to be symptomatic until myxedema supervened.

A number of members of the family had a hereditary abnormality of the skin, hyperkeratosis palmaris et plantaris. Its frequent occurrence in the subjects with myotonia suggests that it may be genetically linked with myotonia in this pedigree.

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Pulmonary Infiltration and Fibrosis of Unknown Etiology

The Risk of Developing Active Pulmonary Tuberculosis

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Introduction

The significance of roentgenographically unchanging pulmonary lesions, in the absence of bacteriologic or pathologic proof of etiology, is difficult to determine.[1] It has been shown by Britten[2,3] that many such cases subsequently develop tuberculosis. The problem of the diagnosis of these cases is of special importance to the Armed Forces where intimate environmental situations exist. It therefore became necessary to assess accurately the risk of such persons developing active pulmonary tuberculosis and thereby becoming sources of infection.

The purpose of this study was to measure the risk among military personnel retained on active duty after clinical study had rendered diagnoses of "infiltration, pulmonary, cause undetermined" or "fibrosis, pulmonary, cause undetermined." These two diagnoses were established in 1948 by a Joint Armed Forces decision[4] in order to afford an orderly classification of unchanging, predominantly noncalcified pulmonary lesions of unknown etiology.

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The opinions or assertions contained herein are the private ones of the authors, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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Material—Selection and Sources

A study group consisting of personnel with the above diagnoses and a control group consisting of personnel diagnosed as having "hemorrhoids" were utilized to determine the risk of tuberculous infection in the two groups, i. e., the incidence rates of tuberculosis.

Both the study and control groups consisted of active duty Naval and Marine Corps personnel who had been admitted to naval medical facilities, clinically studied, and returned to duty during 1951. In order to make the results of the study meaningful, all cases who had had a diagnosis of active tuberculosis during or prior to 1951 were excluded. Also, to determine how many of the remaining personnel developed pulmonary tuberculosis between 1952 and the end of 1954, all cases were excluded who had left the service during 1951 for any reason, e. g., release from active duty, discharge for medical reasons, or death.

There were 268 cases with the diagnosis of "infiltration, pulmonary, cause undetermined" or "fibrosis, pulmonary, cause undetermined" who met the above criteria and were therefore included in the study group. The control group consisted of 493 Naval and Marine Corps personnel, also meeting the above criteria, who were admitted and returned to duty in 1951 with the diagnosis of "hemorrhoids." The members of the control group were selected by means of systematic sampling of the 3436 such cases occurring in 1951.

Cases with the diagnosis of "hemorrhoids" were chosen as the control group because there is no known relationship between hemorrhoids and tuberculosis and because the over-all age distribution of these cases was similar to that of the study group. Both the study and control groups had a generally older population than the U. S. Navy and Marine Corps as a whole,[6] as is shown in Table 1.

TABLE 1.—*Age Distribution of Study and Control Groups and Entire U. S. Navy and Marine Corps, 1951*

Age Group, Yr.	Study Group, %	Control Group, %	U. S. Navy & Marine Corps, %
All ages	100.0	100.0	100.0
Under 20	13.1	8.1	16.8
20-29	51.1	55.8	65.0
30-39	25.0	27.2	14.9
40 & over	10.8	8.9	3.3

TABLE 2.—*Tuberculosis Attack Rates, Study and Control Groups*

Item	Study Group, Pulmonary Fibrosis & Infiltration	Control Group, Hemorrhoids
No. in group	268	493
Man-months of exposure	8,842	16,073
No. cases of active TB	16	0
Attack rate, Cases/1,000 man-months	1.8	0

The percentage of non-Caucasians was slightly higher in the study than in the control group (7.5%, as compared to 4.3%). This difference, however, was found to be not statistically significant.

The sources of information, to determine which persons met the criteria to be included in the study, were the Individual Statistical Report of Patient Cards (NavMed-F) and the personnel records from the Bureau of Naval Personnel and Marine Corps Headquarters. The same sources were used in the follow-up of these cases to determine whether any of them developed tuberculosis during the period of 1952 through 1954 and to determine the dates of discharge of those released from the service during that time.

Statistical Methods

Life tables were constructed for the two groups by utilizing the 1951 date of admission to the hospital as the time of entry into the study and the date of discharge from the service as the date of departure from the study. Each person was credited with one man-month of observation for every entire month spent in the study and with one-half of a man-month for the month he entered and for the month he left the study. By relating the number of cases of tuberculosis developing in each group during the period of the study to the number group, a tuberculosis attack rate for each group of man-months of observation calculated for each was determined (Table 2).

Results

The 493 persons in the control group contributed 16,073 man-months of exposure while in the study. During that time, no members of the control group developed active pulmonary tuberculosis (Table 2).

The 268 persons in the study group contributed 8842 man-months of exposure. Sixteen members of this group developed active pulmonary tuberculosis during the period of the study, yielding a rate of 1.8 cases per 1000 man-months of observation (Table 2). Of these 16 cases, 13 were Caucasian and 3, non-Caucasian. With respect to age, 10 were 30 years of age or older in 1951.

Roentgenologic and Clinical Review of Cases

A review of the x-rays of those personnel included in the study group revealed pulmonary lesions which were localized and contained little or no calcification. In general, no radiologic difference could be seen between those lesions diagnosed as "fibrosis, pulmonary, cause undetermined" and those diagnosed as "infiltration, pulmonary, cause undetermined."

To illustrate this, four of the cases who subsequently developed pulmonary tuberculosis are presented below. Two of them were originally diagnosed as "pulmonary fibrosis" and two, as "pulmonary infiltration." The similarity of the results of clinical investigation and the likeness of the radiologic appearance of the lesions suggested that the separation of such cases into diagnoses of "fibrosis" and "infiltration" was an artificial one and that all such cases could be studied as a single group for the purpose of evaluating the incidence of development of active pulmonary tuberculosis.

Report of Cases

CASE 1.—A 22-year-old Negro man was admitted to a naval hospital in June, 1951, because of a pulmonary lesion discovered on routine photofluorogram (Fig. 1). This roentgenogram revealed an

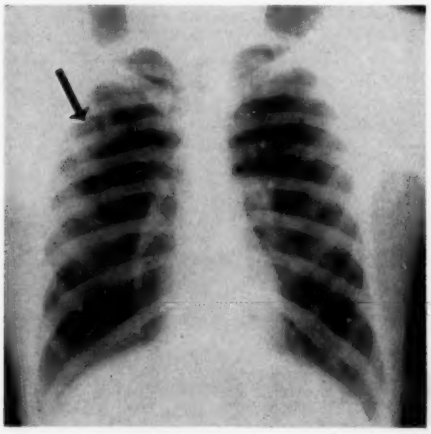


Fig. 1 (Case 1).—Diagnosed as "pulmonary infiltration" in 1951.

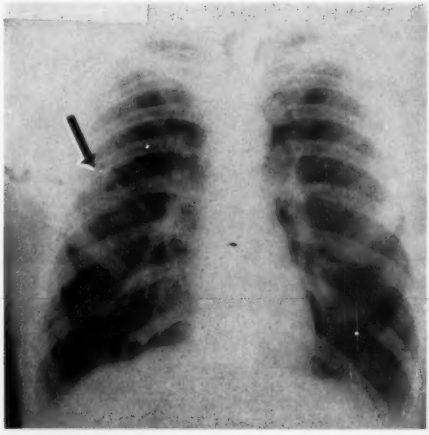


Fig. 2 (Case 2).—Diagnosed as "pulmonary fibrosis" in 1951.

irregular poorly defined noncalcified lesion in the right second anterior interspace and underlying the third rib anteriorly. There were fibrotic strands extending from this lesion to the right hilum. Additional films revealed no evidence of cavitation.

The patient had had frequent upper respiratory infections during his life and occasional night sweats during the previous two years but was otherwise asymptomatic. A chest x-ray taken 18 months earlier was normal. Physical examination and routine laboratory tests revealed no significant findings. Bronchoscopy and tracheal wash cultures for tuberculosis were nonrevealing. The P. P. D. No. 1 and histoplasmin skin tests were positive, while the coccidioidin test was negative. No change in the x-ray appearance of the lesion was noted during the two-month hospitalization, and the patient was returned to duty with the diagnosis of "pulmonary infiltration."

A diagnosis of active minimal tuberculosis was made in February, 1952, on the basis of a positive sputum culture.

Case 2.—A 32-year-old asymptomatic white man was admitted to the hospital in September, 1951, because of a lesion noted on a routine photofluorogram (Fig. 2). This x-ray revealed a conglomerate ill-defined infiltration in the right third anterior interspace, with fibrotic stranding extending to it from the hilum. Laminography revealed small discrete areas of calcification but no evidence of cavitation within the lesion. A chest x-ray 17 months earlier was reported to have been normal. The physical examination and routine laboratory studies were not remarkable. The P. P. D. No. 1 skin test was positive, while the coccidioidin test was negative. After one month of hospitalization the patient was returned to duty with the diagnosis of "pulmonary fibrosis."

In September, 1952 the patient was readmitted to the hospital because of hemoptysis. Sputum cultures were positive for Mycobacterium tuberculosis, and the process was seen to be moderately advanced on x-ray.

Case 3.—A 44-year-old white man was admitted to a naval hospital in August, 1951, because of right pleuritic chest pain of 12 days' duration, which subsided on the day of admission. There had been no other respiratory symptoms or weight loss. X-rays as far back as 1945 were reported to show pulmonary calcifications but were otherwise normal. Physical examination was normal except for a few moist rales over the upper right lung field. An x-ray at the time of admission (Fig. 3) showed a soft mottled infiltrate in the right first and second anterior interspaces. Additional films revealed small scattered calcifications but no cavitation within the lesion. The histoplasmin and coccidioidin skin tests were negative, while the P. P. D. No. 1 test was positive. Acid-fast bacilli were recovered from the sputum on one occasion, but this was considered to be a laboratory error at that time. Serial x-rays remained stable and the patient, asymptomatic during the two and one-half-month period of hospitalization. The patient was returned to duty with the diagnosis of "pulmonary infiltration."

Repeat x-rays at three-month intervals showed no change in the lesion until April, 1952, at which time the patient was admitted to the hospital because of hemoptysis. Radiographic examination at that time revealed an increase in the previously

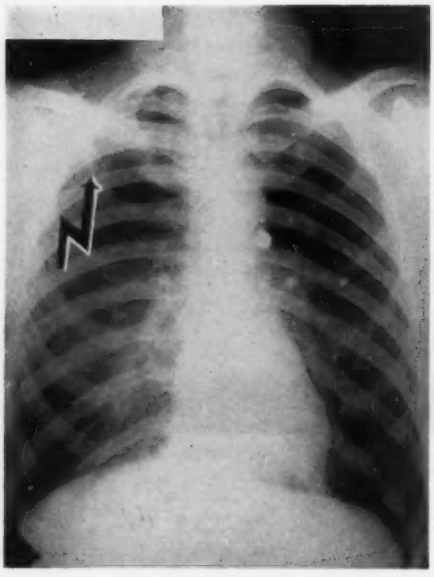


Figure 3

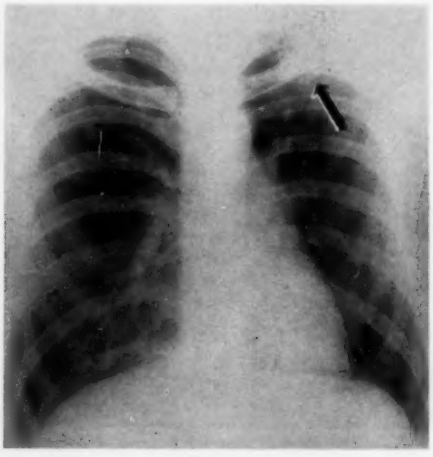


Figure 4

Fig. 3 (Case 3).—Diagnosed as "pulmonary infiltration" in 1951.

Fig. 4 (Case 4).—Diagnosed as "pulmonary fibroses" in 1951.

noted lesion, and a diagnosis of active minimal tuberculosis was subsequently made.

Case 4.—A 31-year-old asymptomatic white man was admitted to the hospital in February, 1951, vealed an ill-defined noncalcified infiltration in the left apex and first anterior interspace. Laminograms showed no evidence of cavitation. There because a routine photofluorogram (Fig. 4) rehad been three previous hospitalizations for the same lesion since 1947, but there had been no apparent change in its radiographic appearance since that time. The physical examination and routine laboratory tests were within normal limits. Four sputa and one gastric culture produced no growth. The histoplasmin and coccidioidin skin tests were negative, while the P. P. D. No. 1 test was positive. The patient was returned to duty after one month of hospitalization with the diagnosis of "pulmonary fibrosis."

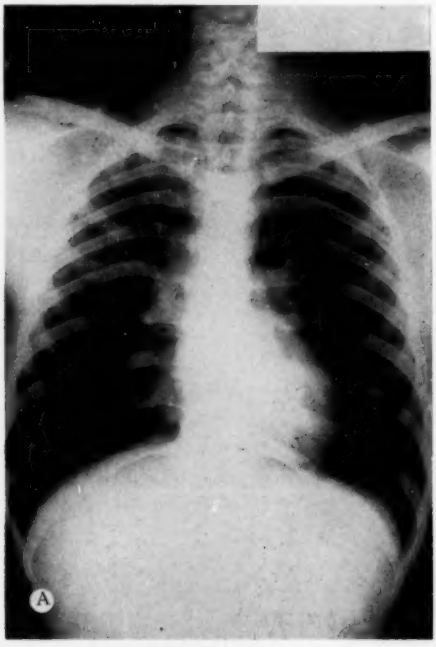
During a readmission to the hospital in October, 1952, for reevaluation of the lesion, a gastric culture produced growth of acid-fast bacilli and the diagnosis of active minimal tuberculosis was made.

Examination of the records and x-rays of those cases who subsequently developed active pulmonary tuberculosis revealed that in every case, the active disease developed in that region of the lung which had been clinically investigated during the 1951 hospital admission.

To illustrate this, two cases are presented below. One shows the radiologic progression in a case returned to duty as "pulmonary fibrosis," and the other, in a case diagnosed as "pulmonary infiltration."

Case 5.—An asymptomatic 21-year-old white man was admitted to a naval hospital in March, 1951, because of a routine photofluorogram revealing a suspicious lesion. A chest x-ray on admission (Fig. 5*A*) revealed a diffuse pulmonary infiltration involving the right first, second, and third anterior interspaces, with no evidence of calcification or cavitation. An x-ray in December, 1949, was considered to be normal. There were no symptoms referable to the respiratory system, but there had been a weight loss of 10 lb. during the previous year. The physical examination and the routine laboratory tests were normal. Three gastric cultures produced no growth. The histoplasmin and coccidioidin skin tests were negative, while the P. P. D. No. 2 test was positive. During the four months of hospitalization the x-rays showed no change in the lesion. The patient remained afebrile and asymptomatic during that time and was returned to duty with the diagnosis of "pulmonary fibrosis."

A routine photofluorogram (Fig. 5*B*) in February, 1952, revealed the previously noted lesion to be more extensive and a new infiltration in the left upper lobe. The patient was therefore readmitted to the hospital, where the diagnosis of active



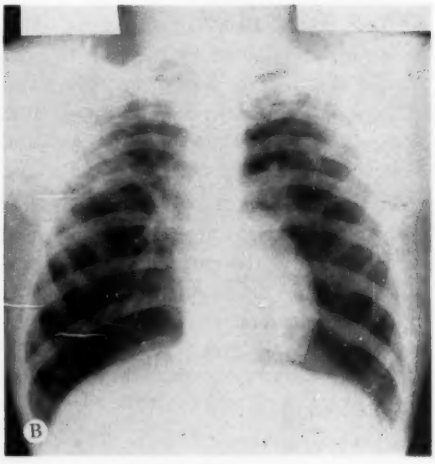


Figure 5

Fig. 5 (Case 5).—*A*, diagnosed as "pulmonary fibroses" in 1951. *B*, moderately advanced tuberculosis, 1952.

moderately advanced tuberculosis was subsequently established.

CASE 6.—A 35-year-old white man, with no symptoms referable to the respiratory system, was admitted to the hospital in July, 1951, because a routine reenlistment photofluorogram revealed a "spot in the left upper lobe." An admission postero-anterior x-ray of the chest (Fig. 6*A*) revealed a lesion behind the left first rib anteriorly. On apical lordotic projection (Fig. 6*B*) the lesion was seen to be a soft-appearing ill-defined noncalcified infiltration extending into the left apex from the superior pole of the hilum. Physical examination and routine laboratory tests were normal. The P. P. D. No. 1 and histoplasmin skin tests were positive, while the coccidioidin test was negative. Repeated sputum and gastric cultures produced no growth. Serial roentgenograms during the two-month hospitalization showed no change in the extent or character of the lesion. The patient was returned to duty with the diagnosis of "pulmonary infiltration."

A routine photofluorogram in March, 1953 (Fig. 6*C*), revealed an increase in the size and confluence of the previously noted lesion in the left upper lobe and the presence of a new infiltration extending into the right first anterior interspace from the hilum. The patient was therefore readmitted to the hospital, where laminograms revealed the presence of a small cavity in the left apex. Gastric cultures were positive for Mycobacterium tuberculosis, and the diagnosis of active moderately advanced tuberculosis was made.

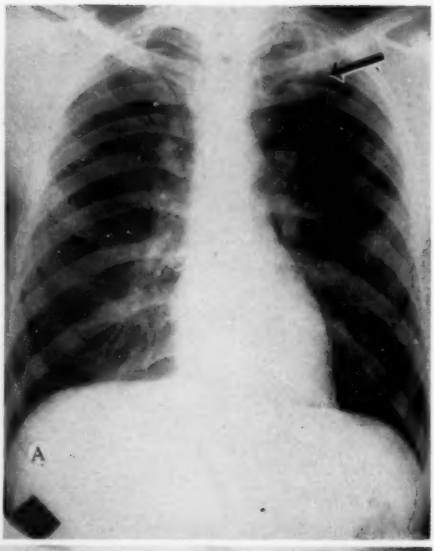
Comment

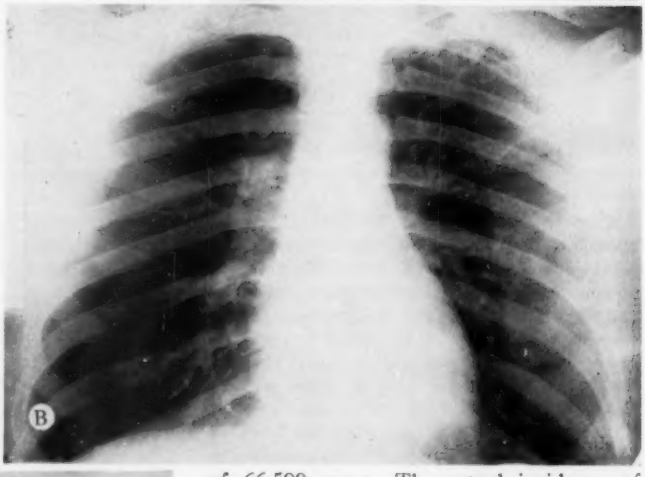
As has been shown, the members of the study and control groups consisted of active duty Naval and Marine Corps personnel, with approximately the same age and race distribution, who were admitted to naval medical facilities and returned to duty in 1951. None of these had a prior history of active tuberculosis. The only gross variable in the two groups, therefore, was the diagnosis with which they were returned to duty. All members of the study group had been discharged from the hospital with a diagnosis representing an "inactive" predominantly noncalcified pulmonary lesion of unknown etiology, while all of those in the control group had been returned to duty with the diagnosis of "hemorrhoids."

If the presence of the pulmonary lesions of the study group bore no relationship to pulmonary tuberculosis, one would expect that the incidence of tuberculosis in the study group would be very nearly the same

as in the control group. When, however, the actual tuberculosis incidence of 1.8 cases per 1000 man-months in the study group is applied to the 16,073 man-months of observation contributed by the control group during the years of study, the *expected incidence* of cases of active tuberculosis in the control group is 29.1, whereas the *actual observed incidence* was zero (Table 3).

Examination of Navy Statistics [6] for the years 1952, 1953 and 1954 revealed 1206 new cases of active pulmonary tuberculosis developing in a population experiencing 36,800,000 man-months of exposure. Applying the study group attack rate of 1.8 cases per 1000 man-months to the man-months contributed by the U. S. Navy during the study, there is an *expected incidence* of 66,590 cases. The actual incidence of 1206 new cases, therefore, represented only 1.8% of the expected cases (Table 3).





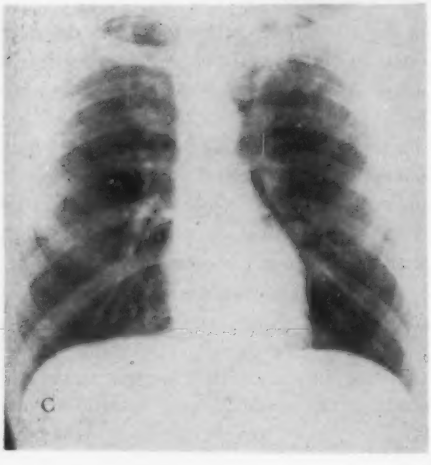


Fig. 6 (Case 6).—*A*, diagnosed as "pulmonary infiltration" in 1951. *B*, apical lordotic view, 1951. *C*, moderately advanced tuberculosis, 1953.

In a recent study by Wier and Tempel,[7] relapses occurred in 4.1% of a selected group of military personnel with active pulmonary tuberculosis who had been treated to the arrested stage and returned to duty by the U. S. Army. Analysis of this group was made for those who had been returned to duty between 1952 and 1955. Tuberculosis occurred in 5.9% of the pulmonary infiltration and fibrosis cases in our study group. While the Army group is not completely comparable to our study group for the purpose of statistical analysis, it is in-

TABLE 3.—*Expected and Observed Cases of Active Pulmonary Tuberculosis, Control Group and U. S. Navy, 1952-1954*

Group	Expected Cases	Observed Cases
Control-hemorrhoids	29	0
U. S. Navy	66,590	1,206

* Expected cases obtained by applying study group attack rate of 1.8 cases per 1,000 man-months.

TABLE 4.—*Occurrence of Active Tuberculosis in Treated Army Cases and Navy Group After Return to Duty*

Group	No. in Study	Developed Tuberculosis	
		No.	% of Total
U. S. Navy and Marine Corps *	268	16	5.9
U. S. Army †	281	11	4.1

* Pulmonary fibrosis and infiltration cases returned to duty in 1951 and followed 1952-1954.

† Arrested tuberculosis cases selectively returned to duty and followed 1952-1955.

teresting to note that the risk of developing active pulmonary tuberculosis in our study group may have been as great or greater than the risk of relapse in the selected Army personnel who had been returned to duty after their tuberculosis had been treated to the arrested stage (Table 4).

Britten [2] determined that of 79 Naval and Marine Corps personnel returned to duty after clinical study in 1949 with diagnoses of pulmonary infiltration or fibrosis, 9 developed pulmonary tuberculosis during the next three years. Our study supports these findings, suggestive of a very high incidence of active pulmonary tuberculosis among such cases.

In view of the demonstrated frequent development of active pulmonary tuberculosis in persons "proven" by clinical study to have predominantly noncalcified "inactive" pulmonary lesions of unknown etiology, the often held concept of the lack of clinical significance of such lesions becomes questionable. In all cases in our study developing active pulmonary tuberculosis, the disease was seen to exist in the area of the lung previously evaluated (e. g., Cases 5 and 6). In several of these cases, the diagnosis of active tuberculosis was made within eight months after the 1951 hospitalization. These facts make it reasonable to assume that many of these cases were actually "missed tuberculosis" in which the diagnosis could not have been definitely made by means of our present clinical and laboratory methods.

Examination of the clinical records revealed that in every case, there had been a thorough evaluation made during the 1951 hospital admission. Incomplete clinical evaluation did not seem, therefore, to account for the abnormally high rate of development of tuberculosis. That it developed at such a high rate, indeed, points up the inadequacy of our present diagnostic armamentarium and, until it is improved, our only means of early detection of tuberculous activity in such cases will continue to be frequent follow-up examinations over a prolonged period of time. To insure adequate follow-up, the establishment of a standardized procedure of examination and a central registry of case reports appears to be desirable.

Since pulmonary tuberculosis is difficult to diagnose in the absence of symptoms and bacteriologic confirmation,[8] there is reluctance on the part of many physicians to make the clinical diagnosis under these conditions. This is understandable, but our study shows that if tuberculous activity is to be detected early and its dissemination thereby kept to a minimum, the physician's index of suspicion must be high in the case of the "stable" predominantly noncalcified pulmonary lesion.

Summary and Conclusions

In order to assess accurately the risk of development of active pulmonary tuberculosis in persons with predominantly noncalcified pulmonary lesions "proven" by clinical study to be "stable" or "inactive," 268 Naval and Marine Corps personnel who

were hospitalized and returned to duty in 1951 with a diagnosis of pulmonary infiltration or fibrosis of unknown etiology were followed for three years, 1952-1954. Sixteen of this group developed active pulmonary tuberculosis.

A control group consisting of 493 Naval and Marine Corps personnel who were hospitalized and returned to duty in 1951 with a diagnosis of "hemorrhoids" were also followed for three years, 1952-1954. No one in this group developed active pulmonary tuberculosis.

Both groups are herein analyzed using the actuarial method. A comparison of the results indicates that the risk of developing active pulmonary tuberculosis in personnel with "stable" or "inactive" predominantly noncalcified pulmonary lesions is markedly greater than in a comparable group of personnel with hemorrhoids.

Application of the tuberculosis attack rate of the study group to the U. S. Navy as a whole during the years of the study shows the observed number of cases of active pulmonary tuberculosis (1206) to be less than 2% of the number expected (66,590).

The development of tuberculosis in the study group is compared to the relapse rate of selected U. S. Army cases of active pulmonary tuberculosis who had been treated to the arrested stage and returned to duty, and is found, in general, to be not very different.

It is concluded that persons in the U. S. Navy, determined by means of present diagnostic methods to have either pulmonary infiltration or fibrosis of unknown etiology, are more likely to have or develop active pulmonary tuberculosis than is now generally appreciated.

Department of the Navy, Bureau of Medicine and Surgery, Washington 25, D. C.

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Observations on Staphylococcus Albus Septicemia in Mice and Men

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Porcelain-white colonies of Staphylococcus albus in cultures from patients usually are dismissed as nonpathogenic commensals or as contaminants. The recent occurrence of S. albus septicemia in three patients after valvulotomy for mitral stenosis led us to reexamine this subject.

Reviews of subacute bacterial endocarditis both in the past and recently show that approximately 1% of cases are caused by S. albus. A survey[36] of cases of staphylococcal bacteremia at this hospital in the years 1936 to 1955 showed that 5 of the 338 cases were caused by this organism. The criteria used for the diagnosis of S. albus septicemia in this study are that the organism should be isolated on two or more occasions from the blood of a sick person with evidence of generalized disease and that no other pathogens should be isolated from the blood. S. albus has for the purpose of this study been accepted as an organism which produces porcelain-white or indifferently colored colonies but never produces a yellow or golden pigment. In the four strains studied in detail mannitol was not fermented and coagulase was not formed.

To the five cases from the records at the University Hospitals from 1936 to 1955 satisfying these criteria we have added three personally treated cases from University Hospitals and one from Ottumwa Hospital in which the responsible organisms have been carefully studied. These patients' records and others in the literature have a distinctive clinical and pathological picture.

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From the Infectious Disease Division of the Department of Internal Medicine and the Department of Bacteriology, State University of Iowa College of Medicine, Iowa City, and Ottumwa Hospital, Ottumwa, Iowa.

Report of Cases

CASE 1.—A white man of 58 developed cramping periumbilical pain one hour after eating food one month before admission. He vomited his food and about a cupful of blood daily and had black stools over a nine-day period. The same thing had happened previously in 1938 and also in 1942. At the latter time he had an operation of unknown type. On admission on Feb. 3, 1943, he was tender in the epigastrium. It was thought he had a peptic ulcer. An x-ray showed a short esophagus and a diaphragmatic hernia. On Feb. 8 he had a temperature of 105.2 F after an intravenous dextrose infusion, and S. albus was isolated from his blood. On Feb. 16 he had an operation to crush the left phrenic nerve. He was discharged on Feb. 20 afebrile. By April 5, 1943, he had gained 19 lb. However, he lost his appetite at the beginning of May of the same year, and by May 12 he had lost 13 lb. His old operation site was tender, and he had a very small hematemesis. On May 13 the left phrenic nerve was crushed again. On May 20 he had a repair of a diaphragmatic hernial sack. On April 12, 1944, he had colicky abdominal pain with vomiting. On April 13 he had a laparotomy and a diagnosis of intestinal obstruction was made. Splenectomy was required because of accidental operative trauma. He was discharged improved on April 25. On June 5 he had a throbbing frontal headache. He complained of nocturia with urgency and thumping pain in the right knee and below the knee to the toes. There were rales in the chest.

He was not seen again until May 28, 1945, when he had been having repeated small hematemasis for one month. Every two to three weeks he was short of breath and had ankle swelling. There were signs of thrombophlebitis. His white cell count was 14,000 per cubic millimeter. On June 7 a blood

culture grew S. albus. He was given an ulcer diet and sent home on June 8. On June 15, 1947, he was found to have a large recurrent hiatus hernia. This was repaired. There was pneumonia in the left lower lobe, with pleural effusion.

On June 23, 1949, he had a shaking chill, with a headache, nausea, and vomiting. He was treated with sulfonamides and penicillin. The next day he was acutely ill, with a very stiff neck. He became psychotic and attempted suicide. He was admitted to this hospital and was found to have a stiff neck. There were moist rales at the right base. The blood pressure was 170/90. Lumbar puncture showed 3935 cells per cubic millimeter in the cerebrospinal fluid, predominantly polymorphonuclear cells. There were Gram-positive cocci in the smear. There was 1+ sugar in his urine. He was treated with penicillin and sulfadiazine and became afebrile by July 4. On this day he had another gastrointestinal hemorrhage; his red blood cell count, previously normal, was 1,900,000, and his hemoglobin was 8 gm. per 100 cc. He had a port-wine-colored urine, and there were no red blood cells, but there was a 4+ Meyer reaction. Bilirubin was 1.8 mg. %; fasting blood sugar was 145 mg. %. There was no evidence of an incompatible transfusion. Blood culture was sterile on July 12, and the culture of the cerebrospinal fluid on June 30 was also sterile. The patient had a second attack of hemoglobinuria. Detailed studies did not reveal the cause. By July 26 he felt well and was afebrile. The hemoglobin was 9 gm. per 100 cc. He was discharged with the diagnosis of acute meningitis of unknown etiology, ulceration of the esophagus with gastrointestinal hemorrhage, and hemoglobinuria of unknown type.

He was seen again in 1951, when he again complained of pain in the epigastrium. He had vomiting, with occasional streaks of blood and occasional attacks of melena. He was afebrile. A posterior wall esophageal ulcer was seen on esophagoscopy. He was treated medically and was sent home improved. This patient has not been seen again.

Case 2.—A 29-year-old hatchery worker was ill in January, 1940, with cough and sputum. He had pneumonia in December, 1941. From 1942 there was increasing shortness of breath and there was orthopnea with loss of weight. He had had some fever and occasional knife-like pains in the right flank. There was swelling of the legs of three to four weeks' duration before admission. He was treated with digitalis without benefit. On examination on admission on March 19, 1943, congestive cardiac failure caused by mitral stenosis was present. There was little peripheral edema. His Wassermann test was negative; his sedimentation rate was 91 mm. in one hour, and there was a trace of albumin in the urine. The electrocardiogram showed A-V block. The red blood cells were 3,700,000 per cubic millimeter; hemoglobin, 11.7 gm. per 100 cc., and the white cell count, 14,000 per cubic millimeter. Urea nitrogen was 11.9 and 13.3 mg. per 100 cc., and creatinine was 1 mg. per 100 cc. on two different occasions. The maximal temperature was 103.8 F. He frequently had a fever, and he was thought to have subacute bacterial endocarditis. Blood cultures were negative on eight occasions and grew S. albus on two occasions. He was treated for cardiac failure, and he died on April 18. At autopsy by Dr. W. S. Pheteplace * the findings were chronic rheumatic endocarditis, with a calcified buttonhole-shaped mitral valve. There was cardiac hypertrophy, hydrothorax, and ascites. There was chronic passive congestion of the viscera, bronchopneumonia, and multiple pulmonary infarcts. The blood was not cultured.

Case 3.—A 68-year-old white laborer was admitted on March 27, 1944, complaining of pain in his abdomen. He had enjoyed good health until one month before admission, when he developed severe stabbing pain in the right upper quadrant. He was given a hypodermic injection and admitted to a hospital at home. He was given enemas and discharged. When admitted to this hospital he had a daily temperature rise to about 102 F orally. There was right upper quadrant pain which gradually subsided. He was mildly dyspneic, with loud inspiratory and expiratory coarse rales throughout the left chest. Extreme tenderness was present in the right upper quadrant. His spleen was palpable and tender. An upper gastrointestinal series showed no abnormality. A colon series was normal, as was an intravenous pyelogram. The gallbladder was nonfunctioning on x-ray. The electrocardiogram was normal. On April 26 an exploratory laparotomy disclosed an abscess involving the gallbladder and duodenum, believed to be the result of a perforated peptic ulcer. This was drained and became infected and was redrained. The patient passed several tarry stools positive for blood on chemical test. He was treated with sulfadiazine and intravenous dextrose. Blood cultures on April 8 and 25 both showed S. albus. The urine on one occasion showed a trace of sugar; otherwise it was normal apart from 8 to 12 white blood cells per high-power field. His hemoglobin was 14 gm. per 100 cc., and the red cell count was 5,500,000 per cubic millimeter. The white cell count was 11,700, 12,900, 22,000, and 17,800 per cubic millimeter between March 27 and May 10. There was some improvement, and he was discharged on June 1, 1944.

* Dr. Emory D. Warner, Professor and Head of the Department of Pathology, provided access to the autopsy records.

He was readmitted on Jan. 8, 1950, and discharged on March 16, 1950. At this time he had had diabetes for two years and was treated for a sore on his heel. He was treated with diet but required no insulin. At this time the diagnoses were arteriosclerosis of both legs with gangrene of the right heel, ventral and inguinal hernias, emphysema, and generalized arteriosclerosis. In September, 1950, he had a supracondylar amputation for gangrene, which he tolerated well. In October, 1952, he had an infection of the left foot and again on this side had a supracondylar amputation and did well postoperatively. He has had no further S. albus infection.

CASE 4.—A 73-year-old white laborer had a perforated peptic ulcer in 1928. He later had a gastroenterostomy and an appendectomy. In 1954 he had progressive weakness and dyspnea. He had a hemoglobin of 3.3 gm. per 100 cc. and a red cell count of 990,000 per cubic millimeter. He was treated with cyanocobalamin (vitamin B_{12}), folic acid, and transfusions; then his hemoglobin became 13.5 gm. per 100 cc. He was admitted three other times in this year. His hemoglobin was 3.1 gm. per 100 cc. and his red cell count, 1,400,000 per cubic millimeter on his admission in November, 1954. He was thought to have septicemia as a result of a transfusion. His fever responded to treatment with erythromycin. He had an attack of acute cholecystitis. Cholecystectomy was done. Senile emphysema and calcification of the aortic valve and a chondroma of the right femur were also found. His hemoglobin was 10.4 gm. per 100 cc. on discharge on Jan. 25, 1955.

On readmission, on March 30, 1955, he had increasing weakness and shortness of breath with chest pain. His temperature was 103 F. He was pale and cyanotic, and he died on April 2, 1955. During this admission his hemoglobin was 4.8 gm. per 100 cc. and his red cell count was 1,720,000 per cubic millimeter. The white cell count was 14,700 per cubic millimeter. Blood cultured on Nov. 10 and twice on Dec. 8, Jan. 13, and April 1, 1955, revealed S. albus. Blood cultures were sterile on Nov. 10, Nov. 23, Nov. 25, Dec. 7, 1954, and March 31, 1955. He was treated with erythromycin, tetracycline, and bacitracin. His B. U. N. rose from 22 to 47 mg. %. The creatinine rose from 1.2 to 2.2 mg. %. The white cell count rose to 24,000. At autopsy (by Dr. F. Aleu) on April 2, 1955, there was severe necrotizing bronchopneumonia and generalized arteriosclerosis, and infarct in the spleen and in the kidney, massive necrosis of the right adrenal, encephalomalacia, a hyperplastic prostate, and testicular atrophy. There was evidence of transfusion hemosiderosis. The heart blood culture was sterile. Escherichia coli was isolated from the lung tissue.

CASE 5.—A 52-year-old white carpenter developed chills and fever three weeks before admission. He was treated with several antibiotics. On admission, on April 14, 1955, he had a temperature of 105 F. His pulse was 104 and irregular. He was stuporous. Many carious teeth were noted. The red cell count was 4,500,000 per cubic millimeter. The hemoglobin was 12 gm. per 100 cc., and the white cell count was 27,150 per cubic millimeter. There was 2+ albumin reaction in the urine, and the urine was full of pus cells and coarse granular casts. A lumbar puncture was normal. The impression at the time was that he was suffering from acute pyelonephritis. He was treated with sulfadiazine. He was very confused and on the fourth day had copious vomiting. Blood cultures grew S. albus on three occasions on April 15, 1955, and twice on April 18. The sensitivities of this organism are shown in Table 3. He was treated with streptomycin and penicillin and later with erythromycin and chloramphenicol (Chloromycetin). He died on the fifth day in hospital. At autopsy, by Dr. C. D. Nordschow, there was acute bacterial endocarditis involving all aortic cusps. There were septic infarcts of the spleen, liver, left kidney, and brain; generalized serosal hemorrhage, and extensive patchy pulmonary hemorrhage. There was isolated myocarditis on the anterior part of the left ventricle. The blood culture was sterile. S. albus along with Proteus and Pseudomonas was isolated from the heart valves.

CASE 6.—In 1949 this 50-year-old woman had disturbance of vision and difficulty in using her left arm. Multiple sclerosis was diagnosed. In 1950 she had sore throat, with aching in the knees, back, and shoulder. One physician believed that at this time she had rheumatic fever. The generalized aching continued intermittently but with some fairly long periods free of discomfort. In January, 1955, she developed a kidney infection after an upper respiratory infection with generalized aching. From February to April she was treated with prednisone (Meticorten), which relieved her symptoms promptly. Because of aching in the back, neck, knees, and shoulders she was seen at the Mayo Clinic in August, 1955. She was found to have a positive Babinski sign on the left and absent abdominal reflexes. The diagnoses of multiple sclerosis and fibrositis were made. In August, 1955, she had irregular menstrual bleeding. A dilatation and curettage removed an endometrial polyp and cured the irregular menstrual bleeding. She was first seen by one of us (K. R. K.) on Dec. 21, 1955, when she complained of generalized itching and intermittent rash over the back and legs. There was no previous history of skin infection or rash. Examination showed enlargement of the liver 3 cm. below the costal margin, with slight

tenderness, a positive Babinski sign on the left, and a distended subdeltoid bursa on the left.

Cultures of the urine revealed an occasional colony of S. albus and S. aureus. A nasal culture grew S. albus and S. aureus. S. albus, S. aureus, and a few α-hemolytic streptococci were cultured from the throat. Blood drawn on the day of admission (Dec. 26) shows S. albus after culture. Other positive blood cultures were obtained on Dec. 27 and 28. Several subsequent ones were negative.

On March 2, 1956, she was treated with potassium penicillin, 1,000,000 units I. M. every 12 hours, and on March 16, with probenecid (Benemid), 5 gm. every 6 hours. On March 17, erythromycin, 500 mg. every six hours, was added to this regimen. This therapy was continued until April 27, 1956, when the penicillin, streptomycin, erythromycin, and probenecid were all discontinued. The bursa continued to form fluid and on April 18 was drained surgically. Cultures of this fluid grew S. albus in abundance. From April 19 to April 30 the left knee was aspirated seven times, and 125,000 units of aqueous potassium penicillin was instilled in the joint. Cultures of the fluid of the left knee revealed S. albus.

On Sept. 10 therapy with novobiocin was started, 500 mg. every six hours. On Sept. 18 she developed a generalized maculopapular eruption, which was very severe and distressing to the patient. The drug was discontinued on that date.

She was readmitted to the hospital on Oct. 1, 1956. An arthrotomy at that time was performed on the left knee, with through-and-through drains. She was discharged on Oct. 24, still having slight drainage from the knee. Blood cultures at this time were negative.

No blood cultures have been made since her last hospital discharge. The patient has been greatly improved, and she does not complain of a generalized aching. The right knee is only slightly painful, and the left knee, although somewhat uncomfortable, has ceased to drain; the arthrotomy wounds have healed, and she has a good range of motion.

Case 7.—This 51-year-old white farmer had no previous history of rheumatic fever, but when examined June 5, 1956, he was found to have pure mitral stenosis with atrial fibrillation at the rate of about 70. His previous history included an episode of cerebrovascular disease in May, 1955. Because of his mitral stenosis a mitral valvuloplasty was carried out on July 17, 1956. He made a good recovery and was discharged home. At home he developed a rash but otherwise felt well. On July 30 he started having severe shaking chills

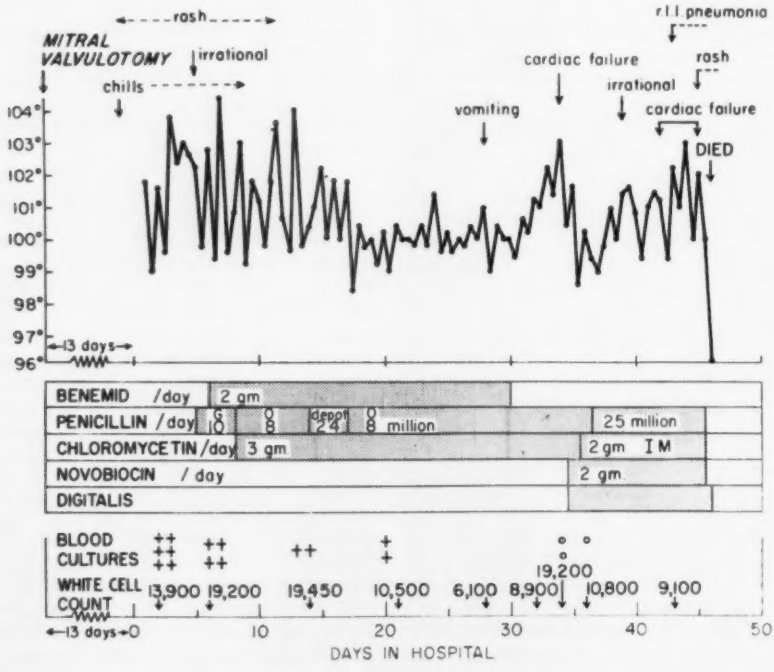

Fig. 1.—The hospital course of a fatal case of S. albus septicemia in a 51-year-old man.

every 12 hours. A day later he was admitted to hospital on the medical service. He had spikes of fever, with temperature up to 104 F. The findings were as before except that fibrillation was more rapid, at 104 per minute, and there was some dullness on percussion and some rales present at the left lung base thought to be a result of the operation. There was no clinical indication of bacterial endocarditis. His course in hospital is shown graphically in Figure 1. Blood cultures on July 31 and Aug. 1, and 3 were all positive for S. albus. On Aug. 5 the patient was first noted to be slightly confused, with faulty memory and a coarse tremor of the hands. These signs recurred intermittently throughout the remainder of the hospital stay. He became afebrile for the first time on Aug. 13. He did well until Aug. 27, when he started to have occasional vomiting. On Sept. 2 his temperature reached a peak of 103 F and he developed frank congestive failure. With treatment he remained out of failure and became afebrile until Sept. 7. At this time his temperature gradually rose; he became irrational and again developed congestive failure associated with pneumonia at the right lower lobe. On Sept. 13 he again developed a rash. Because of anemia (hemoglobin 7 gm. per 100 cc.) he was given a blood transfusion. The following day he became irrational and his temperature was subnormal; he became semistuporous and died the following morning. Unfortunately no permission for a postmortem examination was obtained.

CASE 8.—On Aug. 4, 1956, a 54-year-old white housewife was referred to the University Hospitals because of cardiac enlargement and systolic murmurs. She had a definite history of rheumatic fever at the age of 7. She had had auricular fibrillation since 1951, with recurrent episodes of cardiac failure since 1953. On admission atrial fibrillation with a rate of 72 was present. There was some increase in the venous pressure. The liver was slightly enlarged. There was a trace of pitting edema. Moist rales were heard at the bases of both lungs. The patient was considered to have mitral stenosis and regurgitation, and valvuloplasty was advised. This operation was done on Aug. 7. Four days later she had a temperature of 101 F; blood cultures were taken, and several of them showed S. albus as indicated in Figure 2. She appeared to respond to treatment. On Aug. 10 she had weakness of the left arm and hand and was thought to have a thrombosis or embolus of a branch of the right middle cerebral artery. Starting on Sept. 22 she developed diarrhea. Three stool cultures showed no salmonellae or shigellae, but each contained Candida. Blood cultures on Sept. 26, 27, and 28 were all sterile. On Sept. 4 the hemoglobin had dropped from normal to 9.1 gm. per 100 cc. She was given two blood transfusions. On Oct. 4 the hemoglobin had dropped again from a level of 12.6 gm. % to 7.5 gm. %. She was given another transfusion. During the transfusions she was noted to have some difficulty in breathing and she developed some congestion of the neck veins. The blood was stopped, but the patient died four hours later. There was no evidence of an incompatible blood transfusion. Her hospital course is sum-

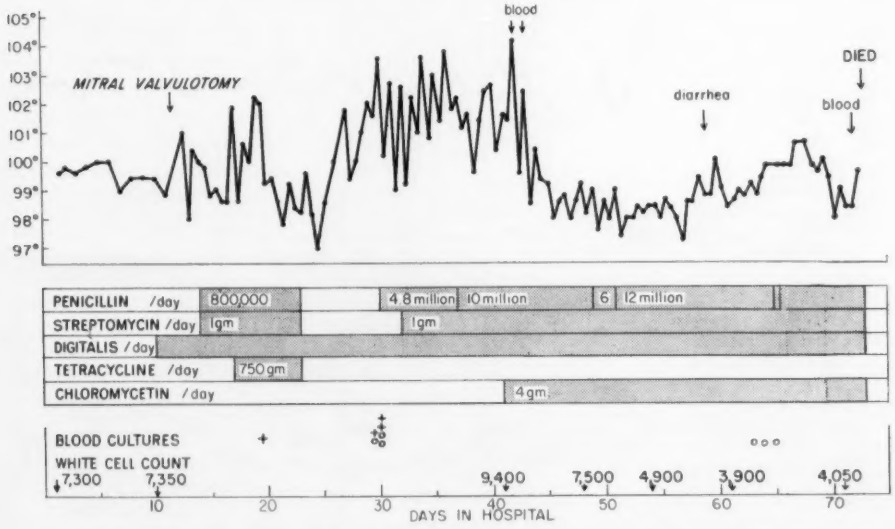

Fig. 2.—The hospital course of a fatal case of S. albus septicemia in a 54-year-old woman.

marized in Figure 2. At autopsy done by Dr. Harris the findings were mitral stenosis with a healed fracture of the valve, evidence of anemia, chronic visceral congestion, and an infarct in the spleen and one in the brain. The autopsy blood culture showed no growth.

CASE 9.—A 43-year-old white housewife was first admitted in April, 1956, with cardiac failure, the result of rheumatic heart disease and atrial fibrillation. She was found to have mitral stenosis, mitral insufficiency, aortic stenosis, and hepatomegaly. She was digitalized, and 6 liters of fluid was removed from the abdomen. On later admission for cardiac catheterization in July she showed marked pulmonary hypertension with evidence suggestive of mitral insufficiency. There was no evidence of a left-to-right shunt. She did well at home until the middle of November, when she noticed fluid collecting in her abdomen, increasing dyspnea, and a gradual increase in weight.

On admission on Jan. 26, 1957, she was pale and orthopneic, with distended neck veins. There were rales at both lung bases and diffuse expiratory wheezes. The heart was regular in rhythm, with a rare premature beat. There was a Grade 3 systolic murmur heard at the fourth and fifth intercostal spaces just to the left of the sternal border. There was also a Grade 2 rumbling apical diastolic murmur. Six liters of fluid was removed from the abdomen. The liver was felt 10 cm. down from the rib margin. She was believed to have mitral stenosis and possibly tricuspid insufficiency with cardiac cirrhosis. Her sulfobromophthalein test showed 16% retention; her alkaline phosphatase was 7.4 units, and the cephalin-cholesterol flocculation test was 2+. With treatment she lost 13 lb. in weight.

A mitral valvulotomy was carried out for mitral stenosis on Feb. 11, 1957. She was noted at this time to also have tricuspid insufficiency. She did well until Feb. 15, when she had a temperature of 103 F. On Feb. 19 she developed chills and a temperature of 104.8 F. Postoperatively she had received penicillin and streptomycin. This was stopped to facilitate diagnosis. Blood drawn on Feb. 16, 1957, and Feb. 22 revealed S. albus on culture. Blood cultures on Feb. 17, 19, 20 (2), 21 (2), and 22 (2) were sterile. On Feb. 22 she appeared moribund, with dyspnea, marked somnolence, ascites, increased venous pressure, and rales on the right side of the chest. She had one spider nevus and some petechiae. The white cell count was 23,900 per cubic millimeter. On the same day her bilirubin was 3.9 mg. %. Blood taken at the time of chills contained S. albus. She responded to treatment with additional digitalis, meralluride (Mercuhydrin), cortisone, novobiocin, and chloramphenicol (Fig. 3). She was found to be deficient in circulating sodium and chloride and responded to 500 cc. of 2% NaCl intravenously. On Feb. 28 mild disorientation was noted, but otherwise she improved steadily. On March 6, five days after

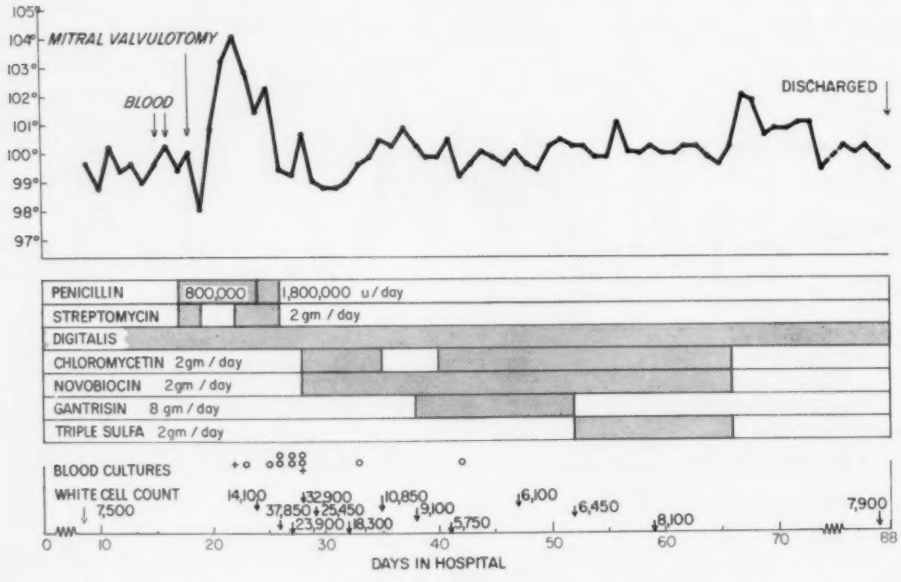

Fig. 3.—The hospital course of a successfully treated case of S. albus septicemia in a 43-year-old woman.

the withdrawal of chloramphenicol, the patient developed petechiae below the site of a tourniquet and two petechiae on the uvula. There was increased cardiac failure. Chloramphenicol was reinstituted, and the patient gradually improved with control of her cardiac failure. Treatment was continued seven weeks. She was observed for three more weeks and then was discharged much improved. She was readmitted to the hospital from May 16 to 20. At this time she was feeling well and had no evidence of recurrence of her bacterial endocarditis. There was no gross cardiac enlargement but definite evidence of moderately severe cardiac cirrhosis. On readmission in July, 1957, the findings were the same. Three blood cultures were sterile.

The Natural History of the Disease—A Review of Forty-Nine Cases

A review of the literature from 1900 has shown over 90 cases of S. albus septicemia.[1,2,4,5,7-29,31,32,34,35,41-46,48-50] In this group we have found 40 cases in which there was sufficient clinical information available for analysis. To this number we have added our nine cases.

This is a serious disease, as 28 of the 49 patients died and 14 of the 18 untreated patients died. This mortality is similar to that of untreated septicemia due to S. aureus.

Predisposing factors are common in the patients with this disease: In this series of 49 cases this occurred in 33 instances. Fourteen had rheumatic fever in the past, and one of these had had a recent operation. Three others had had operations just before the onset of the septicemia. Two of the patients were newborn infants, who are specially susceptible to this infection. Two women had recently delivered, and two had aborted. Two were diabetics, and two had chronic pulmonary tuberculosis. There was one with each of these conditions: severe anemia; coarctation of the aorta; combined whooping cough, measles, and colitis; congestive cardiac failure; combined amebiasis, lung abscess, and duodenal ulcer, and multiple sclerosis. The sexes were affected in a ratio of two males to one female, similar to the sex ratio in septicemia caused by S. aureus.

The clinical picture in this disease resembles more closely a viridans Streptococcus subacute bacterial endocarditis than S. aureus septicemia. Involvement of the cardiovascular system, the respiratory system, and the bones or joints occurred most frequently (Table 1). The symptomatology included dyspnea, cough, and sore throats, in that order. Some complained of pleuritic type pain. The shoulder, knee, and ankle joints were most often painful. In a small number symptoms and signs of congestive cardiac failure were present. A few patients had signs in the lungs discovered on x-ray. Swelling and redness of the joints were rare. In two cases osteolytic lesions were seen on x-ray. The cardiovascular system on examination was found to be involved in two-thirds of the cases. Murmurs were frequently present, most often being systolic in nature and best heard at the apex. Cyanosis occurred only once. In two cases pericardial fluid was noted clinically, and in one a friction rub was heard. The spleen was palpable in about one-quarter of the patients.

Rashes of various types developed. The commonest type was morbilliform and it

TABLE 1.—*The Clinical Findings in Staphylococcus Albus Septicemia*

	No.
Total cases	49
Fever	34
Respiratory system involvement	25
Cardiovascular system involvement	30
Bone and joint involvement	20
Rash	16
Chills	15
Nervous system involvement	14
Palpable spleen	11
Renal involvement	7

TABLE 2.—*The Autopsy Findings in Staphylococcus Albus and Staphylococcus Aureus Septicemia*

Involvement		% of 22 S. Albus Cases		% of 237 S. Aureus Cases *
Respiratory system		46		73
Genitourinary system		46		40
Cardiovascular system		68		25
Spleen		41		9
Brain		18		4
Bone		14		4
Valves involved	A. V.	6	of 15	In 5 cases positive cultures were obtained for S. albus from the valves.
	M. V.	10		
	P. V.	0		
	T. V.	2		

* Reference 36.

TABLE 3.—*Antibiotic Sensitivity of Staphylococcus Albus Strains*

Strain	Antibiotic *											
	T. S.	S. D.	S. S.	Pen.	Strep.	Tet.	Chlor.	Eryth.	Car.	Nov.	Oleand.	Bac.
Ox	R	R	R	R	R	R	S5	R	S10	S5	R	R
St	S1.0	R	R	R	R	R	S5	R	S10	S5	R	S10
Ru	S0.25	S10	S10	S5	S10	S5	S5	S1	S10	S5	S2	S10
Bu	S0.25	S50	S50	R	S10	S5	S5	S1	S10	S5	S2	S10
Sw †	--	--	--	S1	S10	R	S50	S1	--	--	--	--

* Antibiotic concentrations employed: Triple sulfonamide (T. S.) 0.25 mg. and 1.0 mg.; sulfadiazine (S. D.) and sulfisoxisole (S. S.) (Gantrisin) 10, 50, and 250 μg/cc.; penicillin (Pen.) 5 and 10 units/cc.; streptomycin (Strep.) 10 and 100 μg/cc.; tetracycline (Tet.) 5 and 30 μg/cc.; chloramphenicol (Chlor.) (Chloromycetin) 5 and 50 μg/cc.; erythromycin (Eryth.) 1 and 10 μg/cc.; carbomycin (Car.) (Magnamycin) 1 and 10 μg/cc.; novobiocin (Nov.) (Albamycin) 5 and 30 μg/cc.; oleandomycin (Oleand.) 2 and 10 μg/cc., and bacitracin (Bac.) 2 and 10 units/cc. The tests were carried out with sensitivity discs. R indicates resistant; S, sensitive; .., not tested.
† Case 5.

was sometimes mistaken for a drug rash. The latter occurrence could of course not be ruled out. Crops of petechial hemorrhages were noted in a few cases; other rashes were erythematous. In one case there was a rash of pea-sized red-blue lesions which showed S. albus on culture.

Central nervous system involvement occurred in many ways. Delirium, confusion, stiff neck, and hemiplegia were all noted. In the small number of cases with clinical renal involvement a hemorrhagic nephritis was noted. All but 15 of the patients were known to have a temperature usually over 102 F, and many of them had striking severe recurrent chills. Many of the 15 probably also had fever, but it was not mentioned. The white cell count was recorded in 35 cases. It was over 10,000 per cubic millimeter in 24 cases, and in 12 of these it was greater than 20,000 per cubic millimeter. In 14 of the 45 cases studied the hemoglobin was less than 10.5 gm. per 100 cc. or the red blood cell count was less than 3,000,000 per cubic millimeter.

In this series of cases collected from the literature 11 causative organisms were tested for coagulase, 9 being found negative. Of five tested, four were mannitol-negative. Eight strains were hemolytic, and eight were not.

The organisms from Patients 6 and 9 had a similar antibiotic sensitivity spectrum (Table 3), suggestive of a hospital-acquired infection. Serum specimens were available in four of our cases. A low titer of agglutins was present in two, as is shown in Table 4. In other cases in the literature a similar low titer was found. Dassen et al.[9] found a titer of agglutins of 1:50, compared with 1:20 in a control. A hemolysin was present at a titer of 1:64 in Barber's patient,[2] whereas Matthew [23] states that the titer in the patients' blood was higher than in pooled sera. O'Hare and Stevenson [26] found a titer of 1:200 for a bacteriolysin in the patients' serum; it fell after storage.

Experimental Data

Since S. albus is generally considered to be nonpathogenic, it was decided to study the behavior of three strains, Ru (Case 6), Ox (Case 7), and St (Case 8), in young albino Swiss mice. Mortality was observed after injecting the organisms intravenously in varying dosage into groups of 10 mice. An injection of 0.1 cc. of an 18-hour culture of S. aureus in brain-heart infusion broth produces death in at least 1 of 10 animals, with 97% of 100 strains; 0.2 cc. was found to be fatal in almost all cases in a small series.[39] In contrast, deaths occurred in only two experiments, with St organisms, and did not occur with the Ox or Ru organisms (Table 5). There were 10 animals in each group. In fact, we were

TABLE 4.—*Antibody Titers in Homologous Human Sera* *

Strain	Complement Fixation	Agglutination
Ox	Neg.	80 †
St	4	160
Ru	Neg.	Neg.
Bu ‡	Neg.	Neg.
Cord blood	Neg.	Neg.

* Drawn at least 1 month after the onset of illness.
† Reciprocal of serum dilution.
‡ Case 9.

TABLE 5.—*Deaths and Kidney Abscesses in Mice*

Dose of 18-Hr. Culture, Cc.	Ox		St *		Ru *		Smith (Aureus)*	
	Deaths	Abscesses	Deaths	Abscesses	Deaths	Abscesses	Deaths	Abscesses
0.1 I. V.	0	0	0	2	0	0	4	10
0.2 I. V.	0	0	1	0	0	0	10	10
0.4 I. V.	0	0	0	2	0	0	--	--
0.6 I. V.	0	2	1	7	--	--	--	--
0.1 I. P.	0	0	0	0	0	0	10	0
10.0 I. P. †	3	0	5	0	2	0	--	--

* Deaths or kidney abscesses per group of 10.
† Total of injections over a 10-day period.

rarely able to see abscesses of the kidney, which is an almost invariable finding with aureus organisms. It was only after large doses of organisms were injected intraperitoneally that an appreciable number of deaths was found.

The organisms were next injected into animals, and the *survival of the organisms in the various tissues* was studied by previously described methods.[37,38] The organisms were studied from 1 minute after injection through 1 hour, 1 day, 2 days, 3 days, 4 days, 7 days, and 14 days. S. aureus disappeared quickly from the spleen and liver. The number of bacteria remained largely unchanged in the lungs, whereas the organisms multiplied progressively in the kidneys until the animals died. If the animals survived the titer fell in the kidneys. The only difference we could detect with albus strains from aureus strains was a decreased growth in the kidney (Fig. 4). Each point in the graphs indicates the mean titer in three animals.

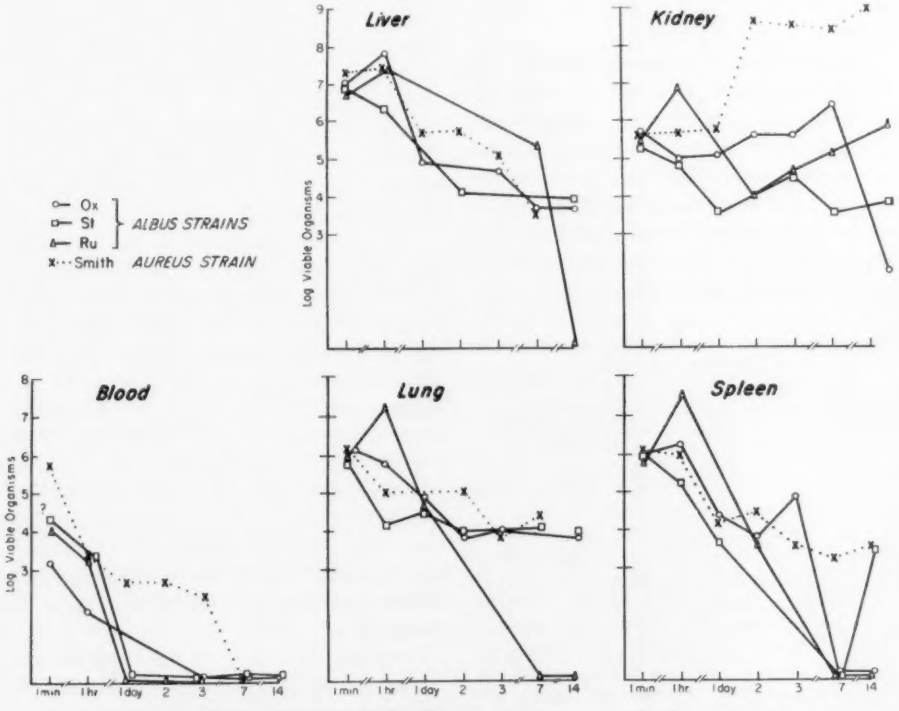

Fig. 4.—Survival of S. albus strains in organs of mice.

Attempts were made to *change the host resistance* of the mice by fasting for 48 hours before infection, by giving cortisone intraperitoneally daily, by operating on them, and by removing their spleens. The last maneuver was done to simulate the postoperative cases in the above series. This operation was controlled by a sham operation where the spleen was pulled out of the abdomen and returned. Operation plus cortisone was tried and sham operation plus cortisone. The fasting was also combined with these procedures. In order to try to simulate the patients with rheumatic fever, animals were anesthetized and small punctures were made of the heart to form small hematomata which might be a suitable area for organisms to grow. This also had no effect. The figures in Table 6 indicate the number of animals having kidney abscesses in a group of 10. The asterisk indicates where death occurred. In general we were not successful in causing more than a slight reduction in host resistance to these organisms.

Passage of the Ox organisms was carried out by intravenous injection in mice followed by recovery of the organism by homogenization of the spleen and reinjection intravenously. This was done for five passages, and then the lethality of the organism in a group of 10 mice was compared with the lethality of the parent strain. There was no enhancement of virulence.

TABLE 6.—*Host Resistance in Mice and Infection with Staphylococcus Albus* *

Treatment	Animals with Kidney Abscesses/No. Group of 10 at Autopsy 14 Days After Infection, No.		
	Ox Strain	Stu Strain	Ru Strain
None	0	2	0
Fasting †	2	0	1
Cortisone ‡	4	1	1
Operation	2 §	4	1
Sham operation	0 §	1	0
Operation + cortisone	0	4	0 §
Sham + cortisone	1	3	0
Operation + cortisone + fasting	1	2 §	0
Sham + cortisone + fasting	0	4	1 §
Heart puncture	1	0 §	0

* 0.1 cc. 18-hour culture I. V.
† Fasted for 48 hours prior to infection.
‡ 25 μg/gm. I. P. per mouse daily.
§ One death.

Animals infected with Ox and St strains died at intervals during a three-month period, but no striking findings were present at autopsy on the survivors.

Filtrates of the Ox strain given intraperitoneally in divided doses up to a total of 7 cc. caused no deaths, and no abnormalities were noted at autopsy.

Comment

It is obvious from the above evidence that cultures of blood showing S. albus cannot always be dismissed as being due to contamination. A second culture should always be taken, since overlooking a bactermia due to this organism may have serious consequences for patients. In a number of cases in our records it seemed likely that this disease was present, but since no confirming culture was taken, they were not included. For example, a 15-year-old school boy developed headache and then evidence of meningitis. S. albus was grown once from his blood, once from a brain abscess at operation, and once from the same site at autopsy. More careful study we believe would have established the diagnosis in more cases.

When the diagnosis of S. albus septicemia is made, it is necessary to determine the in vitro sensitivities of the isolated strain, as these sensitivities differ from strain to strain. As the prognosis of the untreated disease is poor, prompt, carefully chosen, and prolonged antibiotic treatment is recommended. Even with this, death may occur late in the course of the disease, often unexpectedly and even in the face of an apparently sterilized blood stream. Before the sensitivities are known, treatment with novobiocin and chloramphenicol can be recommended, but cases should not be treated without in vitro sensitivity testing to a wide range of antibiotics. At autopsy the vegetations are described as large and friable and clinical evidence of emboli is frequent.

Antibody formation in the blood to this organism is of low titer and inconstant. It does not provide a means of diagnosis.

In the 1957 edition of "Bergey's Manual of Determinative Bacteriology" it is stated: "While Rosenbach describes the orange and the white pus-forming staphylococci of Ogston as two separate species, he states that he finds no difference between them other than the difference in chromogenesis. He describes them under the names *Staphylococcus aureus* and *Staphylococcus albus*. White colonies occur frequently as variants and may be the only type present in a culture. These should not be considered a different species but merely a white variety of *Staphylococcus aureus*. The name *Staphylococcus albus* should never be used for these or for any other white staphylococci." The alternative to S. aureus in *Bergey's Manual* is Staphlyococcus epidermidis, which does not ferment mannitol and is coagulase-negative. However, it is also described as "parasitic rather than pathogenic."

We believe that two distinct differences have been described between aureus and albus strains. They behave differently in living human leukocytes,[33,40] and the albus strains are nonpathogenic or virtually so for rabbits or mice,[48,39] in contrast to the generally lethal effect of the aureus strains.

Numerous observors have described the spontaneous change from aureus to albus in vitro. However, the change from albus to aureus has only been described on three occasions. Pinner and Voldick [30] found that they could convert so-called S. albus to S. aureus by growth of the organisms in anti-albus serum. Byatt and associates [6] claimed to have used extracts of S. aureus with the ability of inducing or stimulating chromogenesis in white strains of the same species. Barber,[3] however, repeated these experiments and confirmed the observation but showed that it was due to chloroform and not to a transforming principle. It is important to note, however, that she was able to isolate golden mutants only from coagulase-positive albus strains under these conditions.

In the light of present knowledge we agree with Wilson and Miles,[47] "Until international agreement has been reached on the classification and nomenclature of these organisms, we think it best to keep the staphylococci separate from the micrococci, and to retain the time honored names of Staphylococcus aureus, Staphylococcus albus and Staphylococcus citreus."

The studies in mice failed to reveal the cause of death. It is probable that relatively high numbers of bacteria are necessary to cause death. It may be that heart valve vegetations provide a protected spot where such high titers can accumulate. Further study of this problem is recommended.

Summary

Case histories of patients suffering from septicemia caused by Staphylococcus albus are described.

The clinical and autopsy findings in these cases and others from the literature are analyzed. The illness often occurs in people with other diseases or predisposing causes. Untreated it is frequently fatal. The disease resembles subacute bacterial endocarditis due to a viridans Streptococcus. Joint pains, chills, and a rash are common. Involvement of the cardiovascular system is frequently found at autopsy. Some patients at the time of death however may have sterile blood cultures.

Experiments with three strains of S. albus obtained from the blood of patients show this organism to grow poorly in the tissues of mice. It rarely kills these animals and seldom produces obvious evidence of disease.

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Addendum

Since this paper was submitted for publication a further staphylococcus albus septicemia has been studied, Case 10. A 53-year-old farmer, a patient of Dr. L. E. January, had been followed since 1954 for rheumatic heart disease and cardiac failure. He had a mitral valvuloplasty in May 1954 complicated by postoperative atrial fibrillation which responded to quinidine. For three years he had definite improvement in his work tolerance and decreased dyspnea. Sixteen months before

admission to hospital in January 1958 he noted the onset of recurrent symptoms of cardiac failure. It was considered that the valve had restenosed and that this might happen after a second valve fracture. Despite this the patient was anxious to have another operation. He did well immediately following a second fracture of the calcified valve cusps on Jan. 15, 1958. However, five days postoperatively he developed anorexia, diarrhea, chills and a temperature of 102 F. A stool culture grew a hemolytic Staphylococcus aureus. Blood cultures on Jan. 20, Feb. 4, 5 and 27 and bone marrow cultures on Feb. 3 and on March 3 grew S. albus. The albus organism was sensitive to novobiocin (Albamycin), erythromycin vancomycin, and chloramphenicol and resistant to triple sulfa, penicillin, streptomycin and tetracycline. On Jan. 27 and 28 blood cultures were sterile. On Jan. 25 an erythematous macular rash was noted on the abdomen which persisted for two days. On Feb. 5, mild jaundice was noted. At this time his bilirubin was 1.1 mg. % at one minute and 2.8 mg. % at thirty minutes. His thymol turbidity was 9.0 units, the zinc turbidity 18.4 units and the cephalin flocculation 4+. The alkaline phosphatase and prothrombin tests were normal. Throughout this period the patient was mentally depressed. His hemoglobin fell from 16 gm. per ml. at the time of the operation to 8 gm. on Feb. 2. He received 5 pints of blood. His white cell count varied between 25,000 and 35,000 per cu. mm. The urine showed only minor abnormalities apart from the presence of bile. On Feb. 27 he started to have chills again. After the first week in March his general condition declined steadily and he died on March 15, 1958. During his postoperative hospital stay he was treated with novobiocin (Albamycin) and streptomycin. The latter was replaced by erythromcyin and all antibiotics were stopped after ten days. When the results of the blood cultures were available he was started on triple sulfa and erythromycin and after a week of this chloramphenicol replaced the triple sulfa. He also received meticorten. After a further 25 days of treatment all previously used antibiotics were stopped and vancomycin was given alone for seven days. In the last three days of life chloramphenicol, triple sulfa and bacitracin were used without success. At autopsy, by Dr. J. Lister, subacute bacterial endocarditis was present. Mitral stenosis (postcommissurotomy), cerebromalacia of the left frontal lobe with hemorrhage and infarcts of the left upper lobe of the lung, spleen and right kidney were also found. A culture at autopsy from vegetations on the mitral valve grew S. albus whereas a blood culture was sterile.

When our albus strains were tested for hemolysis by Elek's plate method, strain Ru produced ε-hemolysin and strains ST and OX did not produce any hemolysin.

Mrs. Jane E. Ryan, Mrs. Martha S. McCutcheon, Mrs. Lois M. Swanson, and Mr. William Shively did the work in the diagnostic laboratories which led to this study, and Mrs. A. B. Vickers and Dr. Ellia Ch. Hazard provided other assistance. The residents on the medical service provided detailed case histories and notes. Dr. J. Roger Porter, Professor and Head, Department of Bacteriology, read an early draft of this manuscript. While he is not in agreement with all the statements made herein, his discussion helped us develop our ideas on this subject.

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The Uricosuric Action of Bishydroxycoumarin (Dicumarol)

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Although the anticoagulant action of bishydroxycoumarin (Dicumarol) has been thoroughly studied, clinically as well as in the laboratory, it is surprising that little attention has been paid to other possible pharmacologic effects of this drug. Some physicians have felt that the drug may have a possible analgetic effect; others believe that treatment with bishydroxycoumarin may increase the speed of resorption of thrombi. Sougin-Mibashan and Horwitz [1] have shown that ethyl biscoumacetate (Tromexan), a related coumarin derivative, increases uric acid excretion. Because of a special interest in patients with arteriosclerotic heart disease who exhibit hyperuricemia, we have investigated the effect of bishydroxyxcoumarin on uric acid excretion. The following is a report of the results of an investigation dealing with the effect of therapeutic doses of bishydroxycoumarin on uric acid excretion and uric acid clearance.

Materials and Methods

Eleven patients were studied: five who suffered from myocardial infarction and three, from thromboembolic disease were undergoing anticoagulant therapy; one patient with gout and three (a healthy person and two ulcer patients) others were given bishydroxycoumarin for the purpose of this study only. Since there was no discernible difference in the response to bishydroxycoumarin, all cases are evaluated as one group.

As far as possible, at least one control period of uric acid clearance was taken for examination before starting bishydroxycoumarin administration.

Bishydroxycoumarin was given in the early evening in doses of from 25 to 200 mg. per day, as required in order to control the prothrombin level of the patient. Urine was collected for periods of 24 hours, starting at 4 a. m., and blood was taken the same morning for uric acid determination. Uric acid content was estimated according to Hepler and Stoskopf's [2] modification of Folin's method; uric acid clearance was calculated according to the following formula:

$$\frac{\text{Urine ur. ac. conc.} \times \text{daily urin. output}}{1440 \times \text{plasma ur. ac. conc.}} = \text{cu. cm/min.}$$

Altogether 18 periods of uric acid clearance were examined without anticoagulant treatment and 103 periods, under the influence of various doses of bishydroxycoumarin. All the clearance determinations were carried out on the same 11 patients.

Results

The results of our examinations are summarized in Tables 1 and 2; Table 3 contains the statistical evaluation of these results. In these Tables, uric acid clearance values are related to bishydroxycoumarin doses given the evening before.

Table 1 gives the average clearance value for each patient for each amount of bishydroxycoumarin administered. It seems evident that in each individual case bishydroxycoumarin increased uric acid excretion and thereby raised uric acid clearance. The basic, i. e., pre-bishydroxycoumarin, values of uric acid in blood and urine varied greatly between our individual cases, no doubt owing to the different state of health and renal function of these patients. In order to compare results obtained in one patient with those obtained in others, we calculated the changes of uric acid clearance as influenced by various amounts of bishydroxycoumarin, in percentages. We arbitrarily called the clearance value determined in each patient after the administration of 50 mg. of bishydroxycoumarin 100%. All the other values were then calculated accord-

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TABLE 1.—*Uric Acid Clearances Following Administration of Various Dosages of Bishydroxycoumarin* *

Case	Dose, Mg. 0 Cl. Periods, No.	0 Cl., %	25 Cl. Periods, No.	25 Cl., %	50 Cl. Periods, No.	50 Cl., %	75 Cl. Periods, No.	75 Cl., %	100 Cl. Periods, No.	100 Cl., %
1	1	5.75	1	6.1	2	6.7	2	8.3	1	9.7
2	1	6.6	2	7.2	3	8.1	1	8.9	3	9.65
3			2	6.7	4	7.7	1	8.9	1	10.2
4			3	7.2	5	7.9	6	9.1	3	9.9
5			4	6.05	8	9.6	3	12.5	2	15.2
6			1	5.9	4	7.2	1	7.75	1	9.45
7	7	7.05			1	7.4	1	10.1	1	10.4
8	1	8.4			12	9.0	4	10.8		
9	3	6.3	3	7.5	3	8.0	2	8.8	2	8.6
10	1	4.6	3	5.8	1	5.5			1	9.6
11	4	4.2			3	5.8			2	10.0

* Values given are averages of all periods tested.

TABLE 2.—*Uric Acid Clearances Following Administration of Various Doses of Bishydroxycoumarin* *

Case	Dose, Mg. 0 Cl. Periods, No.	0 Cl., %	25 Cl. Periods, No.	25 Cl., %	50 Cl. Periods, No.	50 Cl., %	75 Cl. Periods, No.	75 Cl., %	100 Cl. Periods, No.	100 Cl., %
1	1	86	1	91	2	100	2	124	1	145
2	1	81	2	89	3	100	1	110	3	119
3			2	87	4	100	1	116	1	132
4			3	91	5	100	6	119	3	125
5			4	63	8	100	3	130	2	159
6			1	82	4	100	1	108	1	117
7	7	95			1	100	1	137	1	140
8	1	93			12	100	4	120		
9	3	79	3	94	3	100	2	110	2	107
10	1	84	3	96	1	100			1	175
11	4	72			3	100			2	172
Mean		85		85		100		120		136
S. D.		±8.0		±10.6		—		±9.8		±23.7

* Values given are averages of all periods tested.

ingly. The results are given in Table 2. The mean percentage value for the uric acid clearance without bishydroxycoumarin administration was 85%±8 (S. D.) and rose to 146%±23.7 (S. D.) under the influence of 200 mg. of bishydroxycoumarin per day.

Comment

It is evident that bishydroxycoumarin in doses commonly used in anticoagulant therapy exhibits definite uricosuric action. This effect, though, only becomes apparent when the uric acid clearance of a particular day is related to the bishydroxycoumarin dose given the night before. As, on the other hand, our data do not reveal any relationship between the uric acid clearance and the dose of bishydroxycoumarin given the same day, a certain time lag seems to exist until bishydroxycoumarin increases uric acid excretion.

TABLE 3.—*Statistical Evaluation of Table 2*

Bishydroxycoumarin Mg.	S. D.	Diff.	*t*	*P*
0/ 50	2	15	7.5	<0.01
0/ 75	3.4	35	10	<0.01
0/100	6.6	51	7.7	<0.01
25/ 50	2.6	15	4.4	<0.01
25/ 75	3.8	35	9.2	<0.01
25/100	6.6	51	7.7	<0.01
50/ 75	2.6	20	9.7	<0.01
50/100	5.5	36	6.6	<0.01
75/100	6.4	16	2.5	0.02

This effect of the drug as described here raises a number of questions. Most probably the mechanism previously assumed for ethyl biscoumacetate by Sougin-Mibashan and Horwitz [1] is also effective here. They believe that the uricosuric action of this drug is similar to that of dehydroacetic acid, which acts by inhibiting tubular transport. It may be noted that parts of both the ethyl bis-

coumacetate and bishydroxycoumarin molecules bear a structural resemblance to dehydroacetic acid. Uricosuric agents as shown for probenecid, e. g., seem to act by impeding active tubular reabsorption of uric acid (Beyer[3]). Comparison of our data with those obtained for uric acid clearance under the influence of probenecid by others[4] and one of us (J. W. C.) with coworkers[5] show a greater effectiveness of bishydroxycoumarin as uricosuric agent than probenecid, on a weight-for-weight-basis.

The therapeutic significance, if any, of the uricosuric action of bishydroxycoumarin remains to be demonstrated. It may, however, be pointed out that some patients with coronary artery disease may exhibit a hyperuricemia (observations by Gertler et al.[6] and Sougin-Mibashan and Horwitz[1]). The role of this metabolic abnormality in relation to coronary atherosclerosis is not clear. The number of coronary patients showing such hyperuricemia seems to be in our experience by no means negligible. These patients may consequently be subjected to an unforseen but nevertheless important therapeutic influence when given therapy with bishydroxycoumarin. This aspect may be particularly important when the patient receives prolonged anticoagulant treatment. Such treatment may thus favorably influence a metabolic abnormality, the role of which in this disease is still to be elucidated.

Summary

The influence of bishydroxycoumarin (Dicumarol) on renal uric acid clearance has been examined. One hundred eleven clearance periods were studied. It was found that doses of from 25 to 200 mg. of this drug definitely increased uric acid clearance. This effect is proportionate to the dose administered. It can only be demonstrated when a particular clearance period is related to a dose of the drug given a number of hours before the beginning of this period.

The roles of this uricosuric action of bishydroxycoumarin is briefly discussed with reference to those cases of coronary artery disease that exhibit an elevated uric acid level of their blood.

Prof. J. Gross, head of the Department of Experimental Medicine and Cancer Research of the Hebrew University-Hadassah Medical School, reviewed the manuscript. This work was carried out with the aid of a grant from the Teva Middle East Pharmaceutical & Chemical Works Ltd., Jerusalem.

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The Physiological Basis of Neuromuscular Relaxation

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The fundamental role of the hypothalamus and particularly of its sympathetic division in the emotional process has been established by the classical investigations of Bard,[1] Ranson,[2] Hess,[3] and many others. Recent work[4,5] showing that emotional reactions may be evoked by stimulation and ablation of rhinencephalic structures suggests that hypothalamic excitability and emotional reactivity depend not only on reflex stimuli but also corticohypothalamic interrelations.[6,7] Neither these facts nor the finding that impulses from the reticular formation are necessary for the maintenance of hypothalamic excitability and wakefulness[9] have altered the central role which the hypothalamus plays in the emotional process. They seem to imply, however, that changes in hypothalamic excitability may be achieved either via the cortex or through reflexes involving the hypothalamus. The apparent parallelism between the state of excitability of the hypothalamus and emotional reactivity makes an investigation of the factors determining hypothalamic excitability a matter of importance for clinical medicine and neuropsychiatry. The purpose of this paper is to discuss briefly the physiological principles * by which hypothalamic excitability can be lowered. Those procedures which lend themselves to application in the patient are emphasized, and their experimental basis is presented in some detail.[9]

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* The action of the so-called tranquilizing drugs, which according to some authors act directly on the diencephalon, are not considered in this paper.

I. Baroreceptor Reflexes and the Hypothalamus

In 1932, it was shown by Koch[10] that an increase in the pressure of the isolated carotid sinus induced muscular relaxation and even sleep in the unanesthetized dog, whereas a lowering of this pressure was accompanied by a marked increase in neuromuscular excitability, leading in some instances to generalized convulsions. Since it is known that increased pressure in the carotid sinus increases the parasympathetic discharges of the baroreceptors and diminishes reciprocally the sympathetic discharges, it was thought that this shift in the central autonomic balance was primarily responsible for the observed changes in behavior. The finding that increased pressure in the carotid sinus was associated with a lessened responsiveness of the knee jerk seemed to account for the diminished muscle tone and the induction of sleep in Koch's experiment and was interpreted as the result of the "irradiation" of autonomic reflexes in the somatic nervous system.

In studies involving hypothalamic stimulation, it has frequently been observed that the excitability of the sympathetic and somatic nervous system undergoes parallel changes: somatic discharges increase on stimulation of the posterior division of the hypothalamus and diminish on stimulation of its anterior division (Hess). The syndrome observed by Koch on raising the intrasinusal pressure is, therefore, similar to that observed when the sympathetic division of the hypothalamus is reduced in its excitability, as in Ranson's experiments. This author showed that lesions in this area lead to loss of muscle tone and somnolence.[11] The experimental data presented thus far suggest that the action of the

baroreceptors is not confined to the medulla oblongata, as the classical experiments of Heymans [12] and many others indicate, but involve the sympathetic division of the hypothalamus as well. The correctness of this inference and its implications will now be discussed.

The increase in the discharges of the baroreceptors may be achieved in two different ways, either by chemical action on the endings of these receptors or by increasing the pressure in the sinoaortic area.

Protoveratrine has been shown to increase these discharges.[13] As a consequence, the intravenous injection of protoveratrine leads to a fall of the blood pressure, but this effect occurs no longer after the denervation of the sinoaortic area. If our assumption is correct, that baroreceptor reflexes act not only on the autonomic centers of the medulla oblongata but also on the hypothalamus, it should be found that alterations in hypothalamic sympathetic excitability would alter the hypotensive effect of protoveratrine. To test this hypothesis the effect of protoveratrine (0.0005 mg. per kilogram intravenously) on the blood pressure was studied in three groups of lightly anesthetized cats: (*a*) normals; (*b*) animals in which the excitability of the posterior part of the hypothalamus was lowered by the injection of minute quantities of barbiturates close to the mammillary bodies; (*c*) cats in which a part of the sympathetic division of the hypothalamus was destroyed by high frequency coagulation. These procedures were carried out bilaterally.

The experiments showed the expected results.[14] Whereas 11 cats in the control group showed a fall in the blood pressure of 37 mm. Hg, the two experimental groups (10 animals) showed a fall of 5.9 mm. Hg. The difference was highly significant. If cats which had been given intrahypothalamic injections of barbiturates were retested after a time sufficient to allow the effect of the barbiturate on the hypothalamus to wear off (as indicated by the hypothalamic responsiveness to electrical stimulation), the hypotensive action of protoveratrine was restored either partially or completely. The effect of intrahypothalamic coagulation was irreversible. These animals were retested with larger doses of protoveratrine. A hypertensive effect appeared in several animals. Such action of protoveratrine has been previously observed after sinoaortic denervation. The fact that the action of protoveratrine is altered similarly by sinoaortic denervation and by procedures causing a marked reduction in hypothalamic excitability illustrates in an impressive manner the important role which the hypothalamus plays in the baroreceptor reflexes that are elicited by this drug. Since protoveratrine does not produce hypotension in sympathectomized animals, it may be said that the inhibition of the sympathetic system is responsible for the hypotensive action of this drug. In the light of these findings our investigations seem to indicate that the inhibition of the sympathetic division of the hypothalamus plays a decisive role in the reflex originating in the baroreceptors of the sinoaortic area.

An attempt was made to verify this conclusion in another series of experiments in which the action of the epinephrine- and arterenol-induced rise of the blood pressure on the reactivity of the hypothalamus was studied. These drugs increase the baroreceptor discharges by the increase of the blood pressure in the sinoaortic area. Although a diminution in sympathetic reflex excitability during epinephrine-induced rise of the blood pressure was described by Darrow and Gellhorn, in 1939,[15] the systematic investigation of this effect in relation to the hypothalamus is of recent date.[9]

1. *Excitability of Hypothalamus During Arterenol-Induced Rise of the Blood Pressure.*—If in a lightly anesthetized cat the sympathetic division of the hypothalamus is stimulated with square-wave currents or condenser discharges, a measure of the sympathetic excitability of the hypothalamus is obtained by recording the nictitating

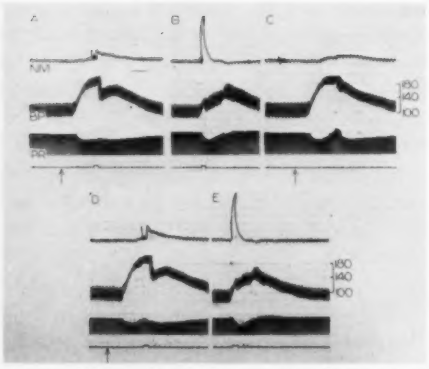


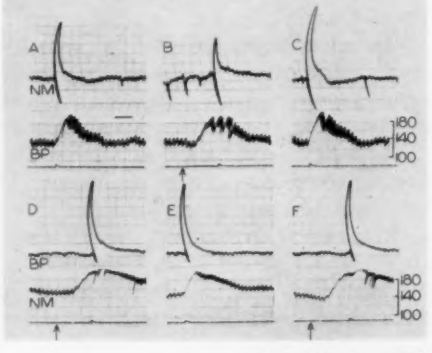
Fig. 1.—The action of a sympathetic hypothalamic stimulus during arterenol-induced tuning. Note the reduction in the size of the contraction of the nictitating membrane (*NM*) and the reversal of the blood pressure (*BP*) effect. Chloralose 85 mg. per kilogram, and urethan, 200 mg. per kilogram. *A*, 2μg. of arterenol I. V. in combination with left posterior hypothalamic stimulation (square wave discharges [S. W. D.], 1.5 volts, 99 pps. 0.4 msec. for 3 sec.). *B*, left posterior hypothalamic stimulation (S. W. D., 1.5 volts, 99 pps, 0.4 msec. for 3 sec.). *C*, 2μg. of arterenol I. V. *D*, 2μg. of arterenol I. V. in combination with hypothalamic stimulation (1.8 volts, 74 pps, 0.8 msec. for 4 sec.). *E*, hypothalamic stimulation as in *D*, by itself.

membrane (NM), the blood pressure, and the heart rate.† Thus, the records *B* and *E* (Fig. 1) show that the stimulation of the hypothalamus under control conditions causes a marked pressor effect, a distinct contraction of the NM, and an acceleration of the heart rate. When, however, this stimulus is applied at the height of the arterenol-induced rise in the blood pressure, a different effect is noted: the changes in the NM and heart rate are minimal and the pressor effect is converted into a depressor action. The lessening of the sympathetic responsiveness of the hypothalamus is obvious and, as Figure 1 shows, reversible. Similar effects are obtained when the blood pressure is raised by epinephrine of other procedures.[9]

That the reduction in sympathetic hypothalamic responsiveness observed during the hypertensive phase resulting from the injection of arterenol and other blood-pressure-raising agents is due to sinoaortic baroreceptor reflexes is indicated by experiments in which the action of arterenol (and related substances) on sympathetic hypothalamic excitability was studied before and after the denervation of the sinoaortic area. It was found that the reduction in sympathetic excitability during the arterenol-induced rise of the blood pressure occurred no longer when the test was performed after the elimination of the sinoaortic baroreceptors.

Figure 2 illustrates a typical experiment. The records *A* to *C* show the results before sinoaortic denervation. It is evident that the contraction of the NM in response to hypothalamic stimulation is decreased when the stimulus is applied during the rise in the blood pressure resulting from the injection of arterenol (compare the height of the NM curve in *B* with the controls in *A* and *C*). On the contrary, when this

Fig. 2.—The action of hypothalamic stimulation during arterenol-induced hypertension (injection indicated by the arrows) before (*A* to *C*) and after sinoaortic denervation (*D* to *F*). Whereas the hypothalamic sympathetic reactivity is reduced in the normal cat during the arterenol-induced pressor effect (see the nictitating membrane in *B*), this effect is abolished after sinoaortic denervation (compare the nictitating membrane in *D* and *F* with the control in *E*). In *D*, read *NM* for *BP* and *BP* for *NM*. Chloralose, 65 mg. per kilogram I. V. *A*, right posterior hypothalamic stimulation (S. W. D., 0.6 volt, 99 pps, 1.6 msec. for 0.5 sec.). *B*, 2μg. of arterenol I. V. in combination with right posterior hypothalamic stimulation. *C*, same as *A*. *D*, 2μg. of arterenol I. V. in combination with right posterior hypothalamic stimulation. *E*, right posterior hypothalamic stimulation, by itself. *F*, 2μg. of arterenol I. V. in combination with right posterior hypothalamic stimulation as in *D*.



† The heart rate (PR) is recorded by a vertical pulse writer. An increase in rate causes a decrease in amplitude and vice versa.

stimulus is applied after sinoaortic denervation (*D* to *F*), the height of contraction of the NM is not decreased but actually increased to a slight extent during the arterenol-induced rise of the blood pressure (compare *D* and *F* with the control in *E*). The cause of this reversal does not concern us here.‡ Suffice it to say that these experiments show that the rise of the blood pressure causes a reduction in sympathetic hypothalamic excitability provided that the receptors in the sinoaortic area are intact. It seems to follow that the rise in the blood pressure produced by arterenol and other drugs[9] elicits baroreceptor reflexes which reduce the excitability of the sympathetic division of the hypothalamus.

2. *Hypothalamic-Cortical System During Arterenol-Induced Rise of Blood Pressure.*

It has been shown in earlier investigations[9,16,17,20] that changes in the state of excitability of the sympathetic division of the hypothalamus are associated with changes in the hypothalamic-cortical discharges and consequently in the action potentials of the cerebral cortex. Thus, the injection of minute quantities of barbiturates in the posterior hypothalamus or lesions confined to this area[16] result in an increase in the grouped (sleep-like) potentials recorded in the electrocorticogram. Conversely, injection of excitatory drugs in this structure reduce or eliminate the grouped cortical potentials which are present in a cat anesthetized with a barbiturate. It was, therefore, expected that the alteration in sympathetic hypothalamic responsiveness induced by arterenol would lead to a reduction in cortical excitability as indicated by characteristic changes in the electrocorticogram.

The electrocorticogram of a "light" cat shows mainly small and frequent potentials. The large, grouped ("Dial"–) potentials are absent. The injection of 1μg.-4μg. of arterenol per kilogram induces during the rise of the blood pressure the appearance of grouped potentials as if barbiturates had been injected in anesthetic concentrations. The action of arterenol was completely reversible and could be demonstrated many times in the same animal.[18]

These experiments were performed not only in normal cats but also in sinoaortic-denervated animals in which the baroreceptor reflexes are eliminated. It was seen that the grouped potentials did not appear in the "denervated" animals on injection of arterenol.

The frequency analysis of the cortical potentials with an Offner analyzer gave further insight into the changes in cortical potentials after the injection of arterenol. This apparatus integrates the potentials varying in frequency between 1 and 30 per second. An increase in excitation is accompanied by a shift to the "right," i. e., the integrated potentials of relatively high frequencies increase in amplitude while those of low frequency decrease. The opposite changes (a shift to the "left") occurs when the cortical excitability decreases.

Figure 3 shows that arterenol causes decreased cortical excitability ("left" shift) in the normal cat but an increase in excitability ("right" shift) after sinoaortic denervation. In some animals in which such

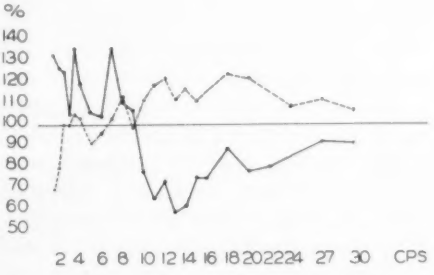


Fig. 3.—The effect of 4μg. of arterenol per kilogram I. V. on the frequency analysis of the motor cortex before (solid line) and after (broken line) sinoaortic denervation. The amplitudes of the control and experimental periods were averaged for each frequency (abscissa), and the numbers obtained in the experimental periods were expressed in percentages of the controls (ordinate). Note that in the normal animal the amplitude of the potentials at low frequencies is increased and that at the high frequencies is diminished after administration of arterenol. After sinoaortic denervation, the effect of arterenol is reversed.

‡ See Reference 9 for further comment.

a reversal did not take place, arterenol failed to cause any change in the frequency spectrum of the cortical potentials after sinoaortic denervation. The experiments may be summarized by stating that the decrease in cortical excitability occurring in normal cats on injection of arterenol depends on sinoaortic reflexes. It is thought that the rise in sinoaortic pressure induced by arterenol leads, via the baroreceptor reflexes, to a lessened excitability of the posterior hypothalamus and consequently to a lessened excitability of the cortex.

Fig. 4.—The effect of succinylcholine on the excitability of the hypothalamus. Note that the sympathetic effect of the hypothalamic stimulation as indicated by the duration of the contraction of the nictitating membrane is reversibly decreased. Stimulation of the posterior hypothalamus (2 volts, 207 pps, 0.8 msec. for 3 sec.). *A*, control stimulus. *B*, same stimulus 55 seconds after 1 mg. of succinylcholine per kilogram I. V. *C*, same stimulus 10 minutes later.

II. Proprioceptive Impulses and the Hypothalamus

In very lightly anesthetized cats proprioceptive impulses are powerful activators of the sympathetic division of the hypothalamus.[19] Their action appears in changes in the hypothalamogram, indicating excitation, and also in diffuse excitatory changes in the cerebral cortex resulting from increased hypothalamic-cortical discharges. These findings suggest that a relaxation of the skeletal musculature is accompanied by a diminution in the state of excitability of the sympathetic division of the hypothalamus and, through a reduction in the hypothalamic-cortical discharges, by a similar reduction in the state of excitability of the cerebral cortex. The action of curare and curare-like substances on the hypothalamus and cerebral cortex was, therefore, studied. In the present work chondodendron tomentosum extract, purified (Intocostrin §), and succinylcholine (Anectine) were used.

In one group of experiments the excitability of the hypothalamus was tested with condenser discharges or square-wave currents before and after administration of these drugs. Figure 4 illustrates the effect of succinylcholine and shows that the sympathetic responsiveness of the hypothalamus to electrical stimulation is markedly diminished, as indicated by the lessened contraction of the sympathetically innervated nictitating membrane. The effect is completely reversible. Attention is called to the fact that this reversibility occurs while the blood pressure is falling to a moderate degree from *A* to *C* of Figure 4. The change in sympathetic reactivity is obviously not related to the progressive changes in the level of the blood pressure.

In other experiments of this group similar results were obtained. The reduced responsiveness of the hypothalamus after administration of chondodendron tomentosum extract appeared frequently also in the form of a lessened pressor effect and in a lessened acceleration of the heart rate in response to the electrical stimulation of the hypothalamus.

In earlier work from this laboratory it was shown that changes in the excitability of the sympathetic division of the hypothalamus are accompanied by parallel changes in the intensity of the hypothalamic-cortical discharges.[9,20] It was, therefore, expected that succinylcholine or chondodendron tomentosum extract would cause significant changes in the EEG electrocorticogram, and this was, indeed, the case. Figure 5 illustrates the profound but reversible changes in the electrocorticogram resulting from the administration of succinylcholine. The excitatory state of the cortex is reduced; large grouped potentials appear in various cortical areas as if barbiturates had been injected intravenously or the hypothalamic excitability had been reduced by the injection of barbiturates into this structure.[9] *These effects take place*

§ Supplied by E. R. Squibb & Sons.

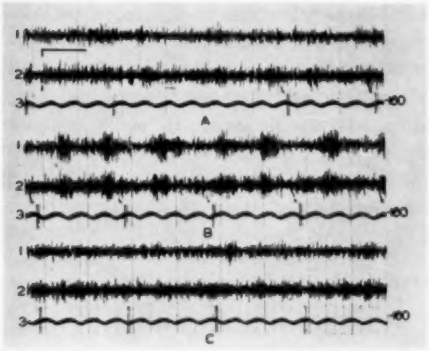


Fig. 5.—The effect of succinylcholine (1.2 mg. per kilogram I. V.) on the electrocorticogram. Note that grouped potentials appear and that this effect is reversible. No significant change of blood pressure. (*1*) Potentials from left and right motor cortex. (*2*) Potentials from left and right auditory cortex. (*3*) Blood pressure. *A*, before injection. *B*, four minutes after injection. *C*, 10 minutes after injection.

although no significant changes in the level of the blood pressure occur (Fig. 5).

In view of the fact that the sympathetic division of the hypothalamus is involved in the emotional process, the emotional behavior of unanesthetized cats was tested under the influence of curare-like drugs. In cats in which electrodes had been implanted into the lateral hypothalamic area the application of an electrical stimulus after the injection of succinylcholine or chondodendron tomentosum extract ‖ produced a diminished sympathetic response, indicated by the lower degree of pupillary dilation, contraction of the nictitating membranes, and piloerection than was observed under control conditions. In addition, changes in emotional behavior occurred; there was a tendency of the slightly curarized cats to withdraw into a corner on stimulation of the hypothalamus, whereas before the administration of this drug aggressive tendencies in response to hypothalamic stimuli prevailed.

Comment

In the preceding section it was shown that the sympathetic division of the hypothalamus can be inhibited by two fundamentally different procedures. One involves increasing discharges from the sinoaortic baroreceptors, and the other, the lessening of proprioceptive impulses. The discharges of the baroreceptors can be increased either by stimulation of the nerve endings of the receptors with suitable drugs such as protoveratrine, or by increasing the pressure in the sinoaortic area. Detailed studies [9] showed that conditions of increased baroreceptor discharges are accompanied not only by lessened reactivity of the posterior hypothalamus but also by increased responsiveness of the anterior hypothalamus. It may, therefore, be said that the diminished reactivity of the sympathetic division of the hypothalamus is the result of reciprocal inhibition. On the other hand, the mechanism demonstrated in the experiments with curare is quite different. The lessened sympathetic reactivity of the posterior hypothalamus results from the elimination or reduction of proprioceptive impulses which contribute importantly to the excitability of the hypothalamus.

In spite of differences in the physiological mechanisms leading to a reduction in hypothalamic reactivity, the two procedures have one important fact in common: the change in the state of the hypothalamus is not restricted to the diencephalon but leads, via the hypothalamic-cortical discharges, to corresponding alterations in the state of excitability of the cerebral cortex.

The reduction in the state of cortical excitation was inferred from the appearance of slow grouped potentials characteristic for sleep and anesthesia with barbiturates. These changes in the electrocorticogram seem to account for the occurrence of sleep when the pressure in the isolated carotid sinus was increased in Koch's experiments and for the reduced emotional reactivity of our cats when as the result of small doses of curare the excitability of the posterior hypothalamus and, consequently, that of the cerebral cortex was reduced.

‖ The doses used were not large enough to interfere with the spontaneous respiration.

The applicability of these findings to human physiology and pathology rests on physiological and clinical observations in man:

1. The extensive work of Jacobson,[21] who emphasizes the occurrence of muscle tension evidenced by the electromyogram (also References 22 and 23) in emotional states. His clinical observations lead him to the conclusion that "emotions subside as the individual *completely* relaxes the striated muscles." Moreover, he finds that muscular relaxation diminishes mental activities.

2. Kleitman's[24] observation that prolonged wakefulness depends on proprioceptive impulses. As soon as the experimental subjects under such conditions were permitted to lie down they fell asleep.

In the light of the experimental work presented in this paper, the lessened emotional reactivity in the state of muscular relaxation appears to be due to the reduced excitability of the sympathetic division of the hypothalamus when proprioceptive impulses are diminished.¶ The tendency to fall asleep in Kleitman's subjects and the lessened ability for mental work in the state of relaxation seem to be the result of the diminished hypothalamic-cortical discharges under these conditions.

The experimental observations reported in this paper suggest that the rise of intrasinusal pressure resulting from the injection of drugs may also be used to accomplish muscular relaxation and to combat, thereby, states of emotional tension. Such drugs must be free from side-effects which increase tension and anxiety. For this reason epinephrine appears to be unsuitable. Preliminary observations (in collaboration with Dr. P. May) give evidence that the injection of arterenol (0.5 mg. intramuscularly) may be useful for this purpose. This test was administered to 47 unselected neuropsychiatric patients (age 20 to 40 years). In spite of the apprehension with which many patients react to the injection of a drug and the continuous recording of the blood pressure for more than 30 minutes, 17 patients said they felt relaxed and 4 fell asleep during the test. In some instances the patients reported that they felt relaxed for the whole day. It remains to be seen whether the induction of a state of relaxation by this procedure is of clinical value.

¶ For further discussion of proprioception and the emotional state see References 9 and 25.

Summary

Physiological experiments show that the excitability of the sympathetic division of the hypothalamus is diminished by (1) procedures leading to increased discharges from the baroreceptors of the sinoaortic area regardless of whether they result from chemical stimulation of the nerve endings with protoveratrine or from mechanical excitation through an increase in the blood pressure following the injection of arterenol; (2) diminution of afferent impulses impinging on the hypothalamus. Since the proprioceptive impulses were found to be powerful stimulators of the hypothalamus, the diminution of proprioceptive impulses through the administration of small doses of curare-like substances (chondodendron tomentosum extract, purified [Intocostrin] and succinylcholine [Anectin]) was studied and found to result in a distinct reduction in sympathetic hypothalamic reactivity. The experiments with curare appear to be physiological models illustrating the mechanism underlying the therapy of relaxation.

It is further shown that the experimentally induced reduction in hypothalamic reactivity is accompanied by diminished hypothalamic-cortical discharges, thereby leading to a state of reduced excitation of the cerebral cortex. The diminished hypothalamic-cortical discharges seem to account for the diminished emotional reactivity and the tendency of the experimental animals to fall asleep under these conditions.

Preliminary observations suggest that arterenol (injected intramuscularly) may induce relaxation and even sleep in man. It is suggested that increased baroreceptor dis-

charges leading to a state of lessened excitability of the sympathetic division of the hypothalamus and, indirectly, of the cerebral cortex are responsible for this effect.

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Hemoglobin H Disease

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Hemoglobin H disease, one of the more recently recognized hemoglobinopathies, is characterized by the presence of hepatosplenomegaly, microcytic hypochromic anemia, intraerythrocytic inclusion bodies, and two hemoglobin components found on electrophoresis—normal hemoglobin and an abnormal component migrating faster than normal hemoglobin. Hemoglobin H disease has been observed in 3 members of a Chinese family,[1] 3 other Chinese,[2] 28 Siamese,[3] 2 unrelated Filipinos,[4] a Greek family,[5] a Cypriot,[6] a Malayan,[7] an Arab from Jordan,[7] 5 Chinese-Indonesians,[8] and a Nepalese Gurkha woman.[2] In this report are presented the clinical, hematological, and family studies of another person of Chinese extraction with hemoglobin H disease.

Report of Case

The propositus* (No. 1) is a 42-year-old Chinese man, fire-control mechanic, with a history of mild to moderate recurrent nonradiating epigastric pain, postprandial bloating, nagging low backache, small stature, and peculiar skin color since childhood. In 1952 the epigastric pain was especially severe, causing him to faint. Gastrointestinal and gallbladder x-rays taken then were normal. At that time anemia was discovered, for which iron was given with no benefit. In 1956 the patient and the rest of his family developed nausea, vomiting, and diarrhea for one week. Over the previous six months the gastrointestinal symptoms and backache had become more noticeable.

The past history was noncontributory, except for occasional episodes of asthma. He had always eaten well and had never used alcohol excessively. There was exposure to solvents at work. At that time he was taking no drugs. The family history was negative, except for a 5-year-old son with asthma. His father, also an asthmatic, died at 88 years, of old age. His mother, age 70; brother, age 49; two sisters, ages 39 and 45; another son, age 3, and daughter, age 1, were all living and well. None of the family members had been diagnosed as having anemia. The systemic review was normal except for three to four bowel movements per day, considered normal by the patient. His appetite was good and weight, stable. The stools were brown and became black when he was taking iron.

On physical examination the patient was smaller and younger-appearing than his stated age. His height was 67 in. and weight, 137 lb. Temperature was 98.7 F; pulse, 80; blood pressure, 120/80. The skin was questionably icteric. The eye, ear, nose, throat, and neck examinations were essentially negative. The heart and lungs were clear to auscultation and percussion. The liver was felt 2 fingerbreadths below the right costal margin and the spleen, 3 fingerbreadths below the left costal margin; neither organ was tender. The rectal examination was negative. The peripheral lymph nodes were not enlarged.

The laboratory studies revealed the findings on urinalysis and serology tests to be normal. The hematologic laboratory tests are listed in the Table. The essential findings were a microcytic hypochromic anemia with slight anisocytosis, poikilocytosis, polychromasia, and target cells (Fig. 1). The differential blood smear revealed segmented cells, 57%; band cells, 6%; metamyelocyte, 1%; eosinophil, 1%; lymphocytes, 32%; and monocytes, 3%. Reticular structures were found in over 90% of the erythrocytes stained with Dameshek's solution. These structures became oval, round, light-blue-staining bodies about a half hour later (Fig. 2). The inclusion bodies varied in size and were found mostly near the periphery of the erythrocyte; they became larger and more prominent after standing for several hours in Dameshek's solution. The inclusion bodies were still present after storage at 4 C for seven days. Approximately 6% of the erythrocytes with reticular structures eventually stained purple with the brilliant cresyl blue dye. Many erythrocytes contained only unstained reticulum; some contained unstained reticulum and inclusion bodies, and others, unstained reticulum, reticulum stained pur-

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* Dr. David L. Pang gave permission for the study report on this patient.

Hematologic Findings of Propositus with Hemoglobin H Disease and Family Members

Family Member, No.	RBC ×10⁶/ Cu. Mm.	Hb., Gm. %	Hematocrit, %	WBC/ Cu. Mm.	Reticulocytes, %	MCV, μ	MCH, μg.	MCHC, %	Hg. Electrophoresis	RBC Inclusion Bodies	F Hb., %*	RBC Osmotic Fragility
1	6.19	10.5	41	5,650	6.0	66.3	17.0	25.6	A+H	+	<2.0	Mod. decreased
2	5.42	16.6	51	4,250	0.6	94.0	32.0	32.0	A	—	0.8	Normal
3	6.35	13.8	49	7,400	0.5	61.3	21.7	28.2	A	—	0.8	Sl. decreased
4	5.28	11.7	43	13,700	0.6	81.4	22.2	27.2	A	—	1.3	Sl. decreased

* Method of Singer, Cherroff, and Singer.[11]

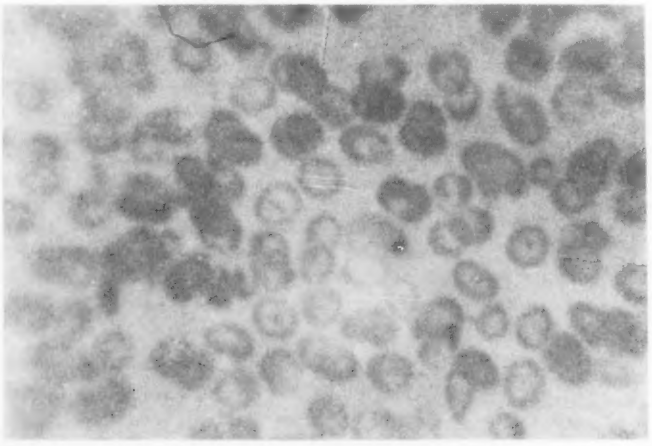


Fig. 1.—Smear of blood from propositus. Note microcytosis, hypochromia, anisocytosis, and target cells. Wright stain; reduced 40% from mag. × 930.

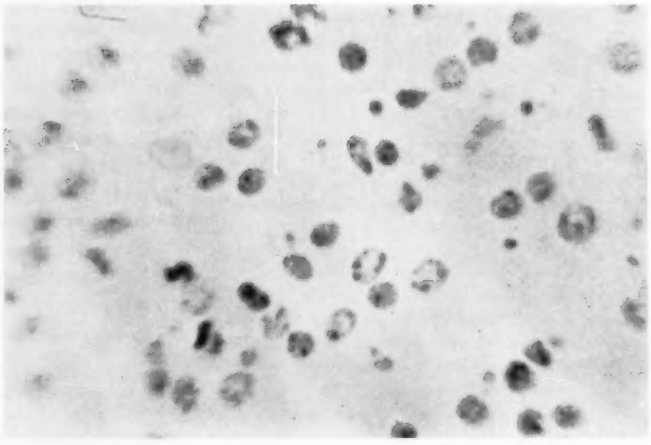


Fig. 2. — Reticulocyte preparation of blood from propositus. The intraerythrocytic inclusion bodies appear as dark round bodies located mostly near the periphery of the RBC. Dameshek's solution; reduced 40% from mag. × 930.

ple, and inclusion bodies. Many erythrocytes contained only inclusion bodies.

The Coombs test was negative. The total serum bilirubin was 3.0 mg. %, with 1.2 mg. % direct-reacting and 1.8 mg. % indirect-reacting. The erythrocyte osmotic fragility revealed increased resistance to hemolysis in hypotonic saline. The serum iron level was 195μg. % (normal range, 50μg.-180μg. %).† The unsaturated iron-binding capacity test was not performed because of turbidity of the serum. The sternal bone marrow examination revealed marked erythroid hyper-

† The serum iron level was determined by Dr. Reubenia Dubach, Department of Medicine (Hematology), Washington University School of Medicine, St. Louis.

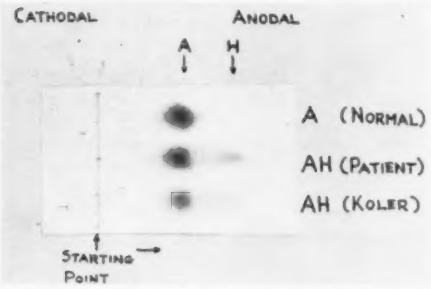


Fig. 3.—Paper electrophoretic pattern of hemoglobin from the propositus, a patient with known hemoglobin H disease (Koler) and a normal person. Barbital (Veronal) buffer, pH 8.8, 0.06 ionic concentration, 350 volts, 30 ma., 5 hr.

plasia involving primarily the normoblastic elements.

Paper electrophoresis of the hemoglobin in barbital (Veronal) buffer (pH 8.8, ionic concentration 0.06) disclosed the presence of two hemoglobin components, a larger amount of normal Type A hemoglobin and a smaller amount of a more rapidly migrating component (Fig. 3). In phosphate buffer (pH 6.5) the larger component (A hemoglobin) migrated to the negative electrode, while the abnormal smaller component migrated to the positive electrode (Fig. 4). The normal component migrated a greater distance from the point of application on the filter paper toward the cathode than the smaller abnormal component, which barely moved beyond the point of application toward the anode. Comparison of the patient's hemoglobin with hemoglobin from a patient with hemoglobin H disease ‡ revealed the normal and abnormal components to have identical mobilities in both alkaline and acid pH buffers (Figs. 3 and 4). Comparison of the patient's hemoglobin with hemoglobin J at pH 8.6 barbital buffer revealed that the abnormal rapid component of the patient migrated faster than J hemoglobin.§ The abnormal hemoglobin component of the patient was still present after 18 days' storage at 4 C and freezing.

The addition of the patient's fresh oxalated plasma to a suspension of normal fresh red cells did not produce inclusion bodies in the normal red cells (stained with Dameshek's solution). The addition of normal fresh oxalated plasma to a suspension of the patient's fresh red cells did not inhibit the formation of inclusion bodies in the latter in Dameshek's solution.

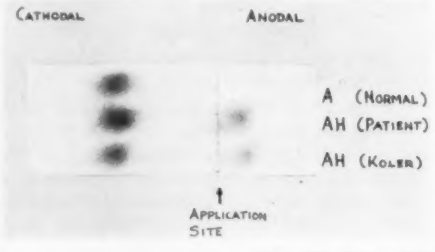
X-rays of the upper gastrointestinal tract, barium enema, gallbladder series, and lumbosacral spine films of the patient were normal except for hepatosplenomegaly. Flat plate of the abdomen revealed an oval 4×5 cm. homogeneous shadow inferior to the right kidney and overlying the psoas muscle, believed to be an enlarged lymph node.

Hematologic studies on family members of the patient are listed in the Table. The brother (No. 2) was clinically, physically, and hematologically normal except for a WBC of 4250. One sister (No. 3) appeared to have thalassemia trait; she was clinically well and did not have hepatosplenomegaly. Another sister (No. 4) was eight months pregnant when studied. Her RBC was 4,520,000, and hemoglobin, 12.5 gm. % during her first month of pregnancy; she appeared to have iron-deficiency anemia. Permission to study the mother and offspring of the patient was denied.

Comment

All of the persons observed to date with hemoglobin H disease, including the patient reported, have displayed similar clinical, genetic, and hematological findings. The clinical symptomatology can be ascribed to the hemolytic anemia or presence of hepatosplenomegaly. The anemia is microcytic hypochromic and associated with reticulocytosis, moderate anisocytosis, poikilocytosis, and target cells. Inclusion bodies or crystals are found in the erythrocytes stained with Dameshek's solution. These inclusion bodies appear light blue in color, vary in size, are generally found near the periphery of the red cell, and become more prominent after

Fig. 4.—Paper electrophoretic pattern of hemoglobins from the propositus, a patient with known hemoglobin H disease (Koler), and a normal person. Phosphate buffer, pH 6.5, 350 volts, 30 ma., 5 hr.



‡ Blood from a patient with hemoglobin H disease was provided by Dr. Robert D. Koler, Division of Experimental Medicine, University of Oregon Medical School, Portland, Ore.

§ Blood from the patient was sent to Dr. Oscar A. Thorup, Assistant Professor of Medicine, University of Virginia Department of Medicine, Charlottesville, Va., for comparison with hemoglobin J on electrophoresis.

storage. The indirect serum bilirubin is elevated; the red cell survival time, shortened, and the erythroid elements of the bone marrow, hyperplastic. The erythrocyte osmotic fragility is decreased in hypotonic saline. Electrophoretic analysis in barbital buffer (pH 8.8) reveals two components, normal A hemoglobin and an abnormal more rapidly migrating component (H hemoglobin). In acid phosphate buffer (pH 6.5) the normal component (hemoglobin A) migrates toward the negative electrode, while the abnormal component (hemoglobin H) moves toward the positive electrode.

The nature of the intraerythrocytic inclusion bodies in hemoglobin H disease is not known. The inclusion bodies appear to correlate with the presence of hemoglobin H pigment and may represent the same substance. Hemoglobin H pigment itself exhibits similar physicochemical properties to normal hemoglobin.[1] The failure of the patient's plasma to induce inclusion bodies in normal red cells in this study would suggest the defect to be intracorpuscular rather than extracorpuscular in origin.

The transmission of hemoglobin H disease is not fully understood. Family studies on hemoglobin H disease suggest the mode of inheritance to be different from previously described abnormal hemoglobin and thalassemic states. Parents of patients with hemoglobin H disease have exhibited the following combinations: (*a*) one parent normal, one parent with thalassemia trait [1]; (*b*) both parents exhibiting thalassemia traits [8]; (*c*) one parent normal, one parent exhibiting hemoglobin H disease,[9] and (*d*) one parent with thalassemia trait, one parent with hemoglobin H disease.[9] Siblings of patients with hemoglobin H disease may reveal no blood changes, morphologic abnormalities compatible with thalassemia, or hemoglobin H disease. Hemoglobin H pigment in the absence of hematologic changes has not been reported, although intraerythrocytic inclusion bodies have been observed in persons with thalassemic blood characteristics who apparently exhibit no hemoglobin H on electrophoresis.[9,10] Whether these latter persons represent the trait form of or mild hemoglobin H disease is not known. To date a preliminary paper electrophoretic survey of 66 Chinese and 55 Filipino healthy blood donors in this study has not disclosed the presence of hemoglobin H pigment.

Genetic studies on hemoglobin H disease thus far would suggest (1) hemoglobin H to be transmitted as a recessive gene where heterozygosity results in no blood changes or a form similar to thalassemia trait and homozygosity, full-blown hemoglobin H disease, or (2) hemoglobin H disease to be combined hemoglobin H thalassemia disease, where hemoglobin H becomes activated and manifest only in the presence of the thalassemia gene.

Summary

The clinical, hematological, and family studies of a Chinese man with hemoglobin H disease are presented. The clinical and hematological findings of the patient presented were similar to previously reported cases of hemoglobin H disease. The essential features included hepatosplenomegaly, microcytic hypochromic anemia, intraerythrocytic inclusion bodies, and the presence of two hemoglobin components on electrophoresis, normal hemoglobin, and an abnormal component migrating ahead of the normal hemoglobin. Attempts to produce inclusion bodies in normal red cells were unsuccessful. Difference in mode of inheritance of hemoglobin H disease from previously described abnormal hemoglobin and thalassemic states is discussed.

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Addendum

Since this article has been submitted for publication, hemoglobin H thalassemia disease has been reported in a 10-year-old Italian boy (Wolff, J. A.; Michaels, R. H., and Von Hofe, F. H.: Hemoglobin H-Thalassemia Disease, Blood 13:492 [May] 1958).

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A Study of Heart Disease in One Hundred Eight Hospitalized Patients Dying with Portal Cirrhosis

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Introduction

The general status of the cardiovascular system in portal cirrhosis has been referred to in many excellent studies. It would appear from these studies that moderate to severe coronary arteriosclerosis is less common in patients with portal cirrhosis up to the age of 55 years than in patients without portal cirrhosis.[5] The incidence of hypertension associated with portal cirrhosis has been recorded as less than that in a similar age group without portal cirrhosis,[3,5,6] although there is not complete agreement on this point.[4] Although not stated implicitly in these studies, it is suggested that serious heart disease may be less common in patients with portal cirrhosis than in the normal population.

Materials and Methods

In order to assess the incidence and type of heart disease in patients with portal cirrhosis, 108 consecutive patients who died with portal cirrhosis and were autopsied were studied. It should be noted that the patients did not all die of complications of portal cirrhosis—only with clinical and laboratory evidence of moderate to severe portal cirrhosis.

The ages of these patients ranged from 26 to 83 years, with a mean age of 57.4 years and a standard deviation of 13.7 years. Twenty-six were women and 82 were men. Presence or absence of heart disease was established by history and physical and laboratory findings plus gross and microscopic examination of the heart. The presence of portal cirrhosis was established by history and physical and laboratory findings plus gross and microscopic examination of the liver.

Results

In 99 cases the heart was accurately weighed after removal of all clots, and hearts weighing more than 400 gm. were considered abnormal. Table 1 shows the heart weight in grams in 99 patients. Figure 1 shows the heart weight by decades in the present series as compared with normal heart weights by decades from a study of Roessle and Roulet[1] and Smith.[2] Inspection of Figure 1 shows a mean heart weight by decades considerably higher in hospitalized patients dying with portal cirrhosis than in those in the normal population.

Table 2 shows the 99 patients classified as to sex, with heart weights exceeding 400 gm. Twenty-four per cent of the women with portal cirrhosis had heart weights of more than 400 gm., while 48% of the men with portal cirrhosis had heart weights of more than 400 gm.

TABLE 1.—*Heart Weight in Ninety-Nine Patients Dying with Portal Cirrhosis*

Heart Weight, Gm.	No.
150-250	6
250-350	34
350-450	29
450-550	13
550-650	10
650-750	4
750-850	2
850-950	1
	99

Mean = 400 gm.
Standard deviation = 122 gm.

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This study was supported in part by a grant from the Wisconsin Heart Association.

Assistant Professor of Pathology (Dr. Lunseth) and Assistant Professor Medicine (Dr. Olmstead), University of North Dakota School of Medicine; Senior Resident in Medicine, Milwaukee County General Hospital, Teaching Associate, Marquette University School of Medicine (Dr. Abboud).

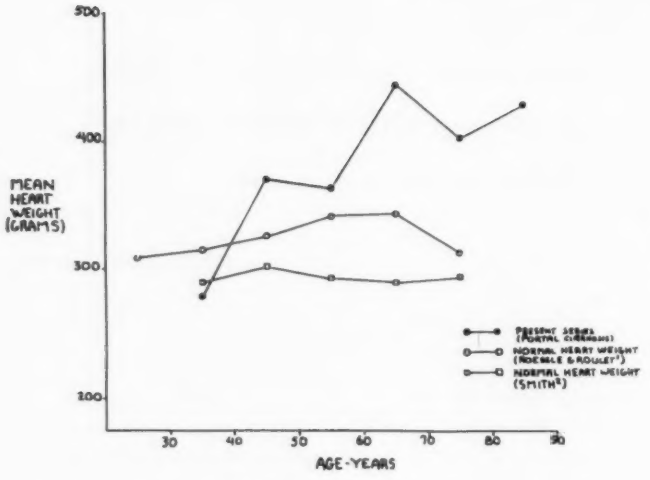

Fig. 1.—Heart weight by decades in normal patients compared with heart weight in patients dying with portal cirrhosis.

Table 3 lists the type of heart disease occurring in these 108 patients with portal cirrhosis. Inspection of the Table shows that about 48% of the 108 patients dying with portal cirrhosis also had associated serious types of heart disease. The 12 patients in the unclassified group were particularly interesting and will be discussed below.

Because of the difference of opinion regarding the incidence of hypertension in portal cirrhosis, Table 4 was constructed to show the blood pressure, heart weights, histopathology of the liver, and causes of death in nine cases of portal cirrhosis accompanied by hypertension of a significant degree. Four of these patients were under 50 years of age, and two of them died of intracranial hemorrhage. Only one (Case 8) had associated severe kidney disease. The finding of eight cases of hypertension without associated kidney disease in 108 cases of patients dying with portal cirrhosis would seem to cause some doubt on the ameliorating effect of portal cirrhosis on hypertension. In this regard our data are more in agreement with Kirschbaum and Shure.[4]

The valvular heart disease in all five patients listed was on a rheumatic basis. Four of these had mitral and aortic involvement, and one patient had mitral involvement alone. There was no syphilitic heart disease in this series.

TABLE 2.—*Heart Weights Exceeding 400 Grams in Patients Dying with Portal Cirrhosis*

	Total No.	No. with Heart Weight over 400 Gm.	%
Women	24	6	25
Men	75	36	48

TABLE 3.—*Types of Heart Disease in 108 Patients Dying with Portal Cirrhosis*

Type of Heart Disease	No.	Total	% of Total
Arteriosclerotic heart disease			
A. Moderate with myocardial fibrosis	15		
B. Severe with myocardial infarction	11	26	24.1
Hypertensive heart disease			
A. Benign essential	5		
B. Arteriosclerotic	3		
C. Malignant phase of benign essential	1	9	8.3
Valvular	5	5	4.6
Congenital	0	0	0
Infectious	0	0	0
Metabolic	0	0	0
Unclassified	12	12	11.2
No heart disease	56	56	51.8
	108	108	100

TABLE 4.—*Portal Cirrhosis and Hypertension*

Case	Age	Maximum B.P.	Classification of Hypertension	Heart Weight, Gm.	Liver	Comments
1	46	220/130	Benign essential	490	1,900 gm., grossly nodular, marked fibrosis throughout portal areas, slight bile duct proliferation, & some lymphocytic infiltration	Known hypertensive for at least 8 yr., died of pontine hemorrhage
2	45	180/120	Benign essential	600	2,970 gm., "hobnail" surface, microscopically distorted architecture, lobular pattern replaced by pseudolobular pattern; marked fibrosis of the portal areas, occasional focus of liver-cell regeneration in the peripheral portion of the pseudolobules	Duration of hypertension unknown; died of cerebral hemorrhage
3	71	180/70	Arteriosclerotic	430	1,150 gm., nodular surface, architecture grossly deranged by irregular circular islands of liver cells surrounded by fibrous tissue	History of asymptomatic hypertension for 5 yr.; died of cerebral thrombosis
4	67	250/149	Benign essential with severe arteriolosclerosis of the kidney.	620	1,700 gm., "hobnail" surface, increased fibrous tissue in portal areas, moderate lymphocytic infiltration	History of hypertension for 2 yr.; myocardial infarction 10 yr. before death; died following spontaneous subarachnoid hemorrhage
5	70	140/100	Arteriosclerotic	450	1,300 gm., nodular surface, marked degeneration of architecture with varying sized lobules; marked fibrosis in portal areas extending between lobules & pseudolobules	Duration of hypertension unknown; died of pneumonia complicated by congestive heart disease
6	44	200/100	Benign essential	650	2,400 gm. nodular surface, marked fibrosis of portal area, distortion of portal triad, some focal areas of round-cell infiltration	Duration of hypertension unknown; died of hepatic insufficiency
7	69	190/100	Arteriosclerotic	350	1,170 gm., marked surface nodularity, marked distortion of normal architecture, increase in fibrous tissue in the portal area with bile duct proliferation; lobules show varying degrees of round-cell infiltration with congestion	Known hypertensive for 12 yr.; died of hemorrhage following ruptured esophageal varices
8	66	170/80	Arteriosclerotic	540	1,200 gm., finely nodular, portal fibrosis with pseudolobular formation; fatty vacuelation of liver cells	Duration of hypertension unknown; died of cerebral thrombosis
9	51	160/94	Benign essential	340	2,130 gm., extremely nodular, marked increase in interlobular & periportal connective tissue; extreme fatty metamorphosis of the liver cells	Duration of hypertension unknown; died in hepatic coma

Cardiac Hypertrophy Associated with Portal Cirrhosis

From a study of 108 patients dying with portal cirrhosis, there were 12 cases with cardiac hypertrophy which could not be accounted for by the usual causes, such as hypertension, valvular disease, and arteriosclerosis. These 12 cases constituted a frequency of 32.4% of cardiac hypertrophy among the 37 cirrhotics of this series who were found to have no clinical or pathological evidence of hypertension or valvular or arteriosclerotic heart disease.

Clinical Picture.—These patients presented with the clinical picture of both heart and liver disease. Shortness of breath, edema of the legs, ascites, and chronic cough occurring in both conditions made difficult the precise assignment of symptoms to either heart or liver in the given case. Paroxysmal nocturnal dyspnea and orthopnea, more typical cardiac symptoms, called attention to the heart disease in two of these patients. The outstanding clinical characteristic of this type of heart disease appears to be the occurrence of cardiac enlargement in the presence of portal cirrhosis and in the absence of known causes for cardiac enlargement, such as hypertension, valvular heart disease, or arteriosclerosis. Seven of these patients had cardiac enlargement demonstrated on either physical ex-

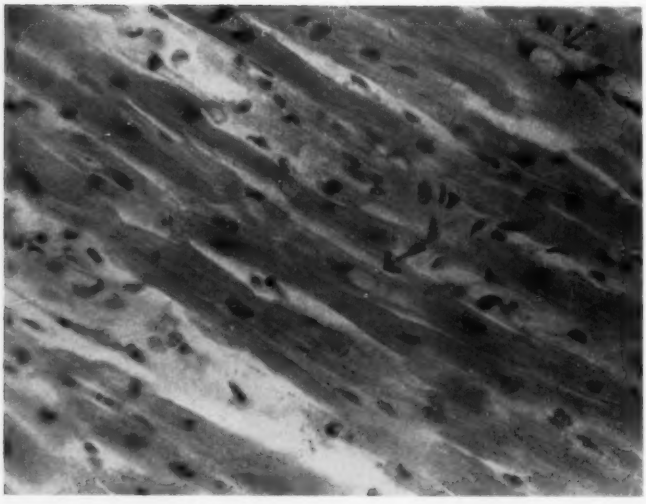

Fig. 2.—Cytoplasmic and nuclear vacuolation. Lower arrow indicates a myocardial fiber with both nuclear and cytoplasmic vacuolation and the upper indicates a fiber with a large nuclear vacuole. Hematoxylin and eosin; reduced about 10% from mag. × 226.

amination or by chest roentgenogram. Tachycardia in the absence of fever or significant anemia should lead one to suspect cardiac involvement associated with portal cirrhosis. Apical systolic murmurs were heard in five of these patients without gross or microscopic evidence of valvular heart disease, and in at least two of these the murmurs were associated with significant anemia.

Electrocardiograms taken in four of these patients showed varying degrees of myocardial anoxia with ST and T wave changes and disturbances characterized by premature auricular or ventricular beats and occasionally intraventricular conduction defect. Two of the patients had auricular fibrillation in the absence of hypertension, arteriosclerosis, or valvular deformities.

Pathological Study of Twelve Cases of Cardiac Hypertrophy Associated with Portal Cirrhosis

Gross Pathology.—The most impressive finding in these 12 cases was the considerable dilatation of the ventricles, especially the right, and the decreased myocardial consistence. Grossly visible scarring was found in only two cases; these had the two heaviest hearts (over 600 gm.). The scarring was confined to the inner one-half of the left ventricular wall, and the scars were not larger than 0.3 cm. Subendocardial hemorrhages were found in three cases. In each case they were on the upper middle portion of the left side of the interventricular septum and measured no more than 0.8 cm. in greatest diameter. The coronary arteries were carefully dissected in all the cases and found to be completely patent and to show only minimal arteriosclerosis. The valves in all cases were free of deformity.

Histopathology.—In all 12 cases the myocardial fibers were swollen; the swelling was most marked next to the endocardium and the Thebesian vessels. Cytoplasmic and nuclear vacuolation (Fig. 2) and perinuclear brown pigmentation were greater than that usually seen in other forms of cardiac hypertrophy. The brown pigment did not differ qualitatively from that found in hypertrophic hearts of noncirrhotics. It did not stain with Prussian blue and was only faintly and inconstantly acid-fast and sudanophilic; therefore, it was considered to be lipofuscin. In these hypertrophic hearts of cirrhotics there was more muscle fragmentation and greater obscurement of the muscle striations than is usually seen in hypertrophic hearts of noncirrhotics. Myo-

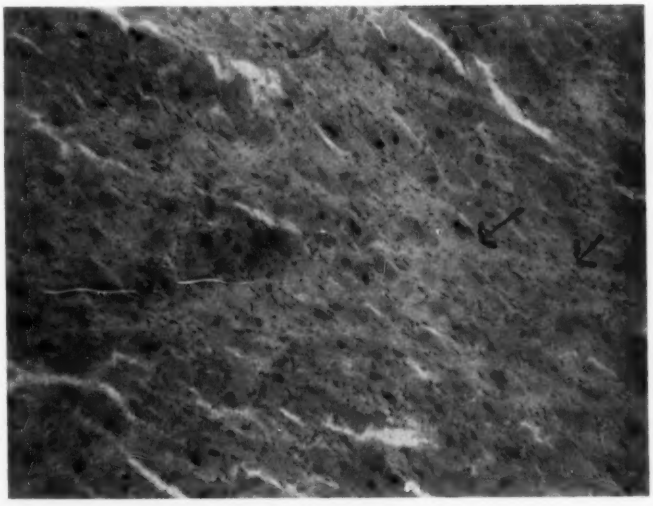

Fig. 3.—Diffuse and delicate fibrosis. Note partial and segmental fibrosis of many of the fibers. The arrows indicate lines of fibrous tissue bridging the gap between transversely ruptured muscle fibers. Hematoxylin and eosin; reduced about 10% from mag. × 42.

cardial fibrosis was more delicate and diffuse and usually more widespread (Fig. 3). Dense myocardial scars several fibers wide, which are frequently seen in cardiac hypertrophy due to hypertension or arteriosclerosis, were infrequent in these cases. Often the fibrosis involved only a segment of muscle fiber (Fig. 4). In some areas it appeared as if this segmental fibrosis consisted of a deposition of collagen in the framework of myofibrils segmentally denuded of sarcoplasm. In other areas this segmental fibrosis was only apparent and actually consisted of only denuded myofibrils (Fig. 4). Frequently noted was the interposition of delicate fibrous tissue in the gap caused by transversely ruptured muscle fibers (Figs. 3 and 5).

Exudation sufficient to indicate true myocarditis was present in only two cases. In both it was diffuse and dense and largely lymphocytic and histocytic (Figs. 6 and 7).

Fig. 4.—Segmental fibrosis of muscle fibers. The arrow indicates an area where the denuded myofibrils can be seen. Hematoxylin and eosin; reduced about 10% from mag. × 226.

Fig. 5.—Interposition of young fibrous tissue between the fragments of transversely ruptured muscle fibers. Hematoxylin and eosin; reduced about 10% from mag. × 266.

It was not accompanied by undue muscle necrosis and showed no predilection for blood vessels. In neither of these cases was there found any infection which might explain the myocarditis, nor was there a history of ingesting of toxin other than alcohol.

*Relation Between Degree of Cirrhosis * and Cardiac Weight.*—The possibility was considered that the cardiac weight might be less in the advanced stages of cirrhosis than in the earlier stages. Such a consideration was prompted by the fact that intrahepatic, portal, and hepatic veins become progressively obstructed and effaced as cirrhosis advances.[7,8] Consequently, hepatic blood flow becomes reduced,[9,10] with the possible result that blood flow to the right heart and cardiac output are reduced. As a means of

* By the degree of cirrhosis is meant the amount of pseudolobular regeneration, the amount of fibrosis, and the degree to which the intrahepatic, portal, and hepatic veins have become compressed, narrowed, or effaced.

Fig. 6.—Typical area of diffuse and dense intercellular infiltrate in one of the cases with myocarditis. Hematoxylin and eosin; reduced about 10% from mag. × 42.

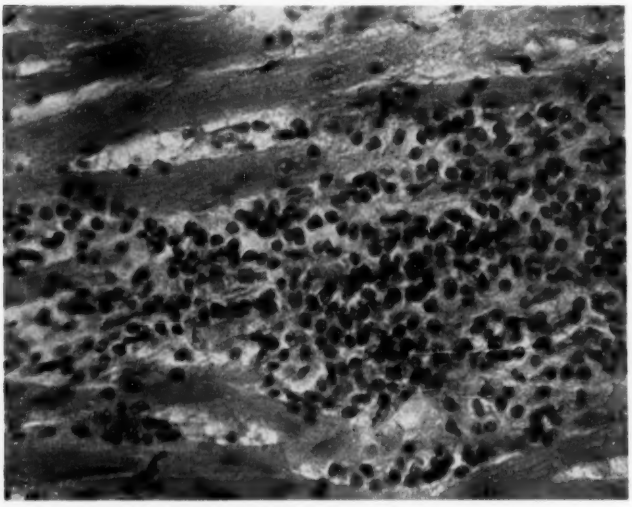

Fig. 7. — High-power view of exudate shown in Figure 6, showing the predominance of histiocytes and lymphocytes. Hematoxylin and eosin; reduced about 10% from mag. × 226.

investigating this possibility, all the cases from the entire series of 108 cases which had no clinical or pathologic evidence of arteriosclerotic, hypertensive, or valvular heart disease or other classified forms of heart disease were studied in terms of the cardiac weight and degree of cirrhosis.

Thirty-seven cases were found in which there was sufficient tissue for accurate evaluation of the cirrhosis and enough data for ruling out known types of heart disease. These included the 12 cases with cardiac hypertrophy previously described.

Of the 25 cirrhotics without cardiac hypertrophy, 5 (20%) had early cirrhosis, 8 (32%) had moderately advanced cirrhosis, and 12 (48%) had far-advanced cirrhosis. Of the 12 cirrhotics with cardiac hypertrophy, 4 (33.3%) had early cirrhosis, 5 (41.1%) had moderately advanced cirrhosis, and 3 (25%) had advanced cirrhosis. Still another way of expressing the data shows that of the 22 cases with early or moderately advanced cirrhosis 9 (41%) had cardiac hypertrophy, while of the 15 cases with far advanced cirrhosis only 3 (20%) had cardiac hypertrophy. The data indicate a significantly greater frequency of cardiac hypertrophy among the early and moderately advanced cirrhotics than among the advanced cirrhotics.

Comment

The pathologic changes accompanying the cardiac hypertrophy in these 12 cases of portal cirrhosis did not differ qualitatively from those accompanying cardiac hypertrophy due to hypertension or valvular disease in noncirrhotics; rather, the differences were quantitative. Ventricular dilatation was greater and myocardial consistence was more reduced in the cases associated with cirrhosis and histologically there was greater nuclear and cytoplasmic vacuolation and more perinuclear pigmentation with lipofuscin. Fibrosis in these hearts was more delicate and diffuse, frequently involving only small segmental portions of a fiber. In some areas what appeared to be fibrosis was in fact clusters of myofibrils denuded of sarcoplasm. In some places collagen was deposited on a framework of denuded myofibrils. The frequent isolated degeneration and fibrosis of single fibers or even parts of single fibers suggests that these changes might be due to causes inherent in the fiber rather than to reduced blood supply. In the latter case the foci of degeneration of fibrosis consisting of several fibers are frequent.

The fibrous bridging between the transversely ruptured fibers indicates that muscle fragmentation occurred a considerable time

before the agonal state and perhaps the fragmentation was the result of the severe cardiac dilatation found in these cases. These bridges probably served as insertions for the muscle fragments, thus allowing them to retain at least some degree of function. It is conceivable that this fibrous bridging might have interfered with normal myocardial contraction, thus adding to the work of the heart and perhaps contributing to the cardiac hypertrophy. The predominantly lymphocytic and histiocytic exudate found in the two cases with diffuse interstitial myocarditis was similar to that reported in some of beriberi heart disease.[11,12] Apart from the myocarditis these cases did not differ clinically or pathologically from the other 10 cases.

Perhaps the most important cause of the cardiac hypertrophy in cirrhosis is the increased cardiac output which had been reported in cirrhotics.[13,14] This is produced by a greater stroke volume in response to extreme vasodilatation.[14] The possibility has been considered that this vasodilatation is the result of the inability of the anoxic cirrhotic liver to detoxify VDR, a vasodilating substance produced by the liver and normally detoxified by it.[14,15] This pathogenesis was first offered by Weiss and Wilkins for their cases of nutritional heart disease,[16] often called occidental beriberi heart disease.[17] In these cases they also found a considerable increase in cardiac output and a great increase in the velocity of blood flow, both of which they attributed to vasodilatation. They considered the vasodilatation as being due to the effect of thiamine deficiency on the central nervous system. Since all 12 of our cases were severe alcoholics, it is possible that the same etiological factors present in the cases of nutritional heart disease of Weiss and Wilkins also obtained in our cases.

One of the most salient findings in this study was the fact that the idiopathic cardiac hypertrophy was significantly more frequent in the early and moderately advanced cirrhosis than in the far-advanced cirrhosis. In the latter the heart weight was usually normal and frequently less than normal. Possible corroboration of this fact was found in the results obtained at this hospital by Huston in a circulatory study on cirrhotics.[18] He found that in cases clinically classified as moderately advanced cirrhosis the cardiac output was normal or reduced. An explanation for this phenomenon might be the progressive alteration of the hepatic veins by the regenerative parenchymal nodules and narrowing and effacement of their lumens by the fibrosis.[7,8] If this mechanism reduces the blood flow through the liver enough to interfere with cardiac output, then such an interference could possibly compensate for the factors increasing cardiac output, and a heart which might have been hypertrophic in the early stages of cirrhosis might revert to normal weight in the advanced stage of cirrhosis.[19]

Summary and Conclusions

The cardiovascular status is evaluated clinically and pathologically in 108 hospitalized patients dying with portal cirrhosis.

Fifty-two (48%) of these one hundred eight patients had associated serious heart disease. Of these, 26 had arteriosclerotic heart disease, 9 had hypertensive heart disease, 5 had valvular heart disease, and 12 had cardiac hypertrophy.

Cardiac hypertrophy occurring in portal cirrhosis was characterized by signs and symptoms of congestive heart failure, cardiac enlargement without obvious cause, tachycardia, apical systolic murmurs, and electrocardiographic evidence of premature auricular and ventricular contractions and varying degree of intraventricular conduction defects.

Pathological study of the heart and liver of the patients with cardiac hypertrophy showed that in 9 of the 12 patients the accompanying portal cirrhosis was early or only moderately advanced. It is suggested that the cardiac hypertrophy in these cases was due to the increased cardiac output as-

sociated with peripheral vasodilatation in the early stages of portal cirrhosis.

This study suggests that patients with portal cirrhosis have not only the common types of heart disease but are also prone to develop an idiopathic type of heart disease associated with the portal cirrhosis per se.

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Sarcoidosis of the Spinal Cord

Report of a Case with Remission Associated with Cortisone Therapy

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Sarcodosis is a relatively common disease, but involvement of the nervous system is rare and involvement of the spinal cord is almost a curiosity. Colover,[2] in reviewing the world literature, found 115 cases of involvement of the nervous system and added 3 of his own. In the majority of these cases, uveoparotid fever was present with paralysis or paresis of the facial nerve. However, other cranial nerves, peripheral nerves, meninges, pituitary, hypothalamus, and brain were sometimes affected. Changes in the cerebrospinal fluid have repeatedly been reported. Occasionally, the syndrome of Guillain-Barré has been observed.

Colover found only one case of involvement of the spinal cord. This case was described by Reisner,[8] who mentions among 35 cases of Boeck's sarcoidosis "one male negro patient who presented findings pointing to a lesion in the sacral segment of the spinal cord. Complete disappearance of the neurological symptoms occurred in the course of observation." Dr. Reisner has given me the following supplementary information about this case.

In 1933, at the age of 38, the patient was found to suffer from chronic uveitis. This eventually led to phthisis bulbi and blindness in one eye. At that time the eye involvement was thought to have been on a tuberculous basis, and an enucleation was performed. In 1937 he developed numbness in the perianal region, constipation, urinary difficulty, dizziness, and occasional staggering of gait. He was exhaustively studied, and "an expanding lesion, possibly multiple, affecting the sacral segment of the spinal cord" possibly due to a tuberculoma, was diagnosed.

When in 1940 the patient came under Reisner's observation, all the symptoms and signs pointing to the cord involvement had disappeared. He then, however, presented unmistakable evidence of systemic sarcoidosis, including involvement of the superficial and thoracic lymph nodes, of the lungs, and of the mucosa of the upper respiratory tract. The preceding uveitis seemed to fit well with this diagnosis. Biopsy of an epitrochlear lymph node and of the nasal mucosa revealed the presence of Boeck's sarcoidosis.

Six months later, in August, 1940, the patient died. The autopsy showed terminal generalized tuberculosis, including tuberculous meningitis, as well as extensive sarcoid lesions throughout the organs, in the stage of hyalinization. In the autopsy protocol microscopic examination of the spinal cord was not mentioned. Since at that time corticosteroids were not yet available, it seems probable that the regression of the cord lesion must have been spontaneous.

I have found seven other cases in the English, French, and German literature. Erickson, Odom, and Stern[4] reported a case of fatal cerebral involvement without spinal cord symptoms. At autopsy, however, in addition to the changes in brain and medulla, "the cervical, thoracic and lumbar regions of the spinal cord were observed to contain patchy infiltrations of a similar nature but much less intense than those in the brain stem."

Pennell[7] reported three cases of nervous system sarcoidosis, one of which affected

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the spinal cord. This patient had glandular, pulmonary, and uveal involvement as well as spinal cord symptoms and signs, located at the level of the second thoracic segment. Cortisone was given without benefit.

Zeman [10] reported a case of a 53-year-old woman with Boeck's sarcoidosis and spastic paraplegia which had been mistaken for multiple sclerosis.

One of Siltzbach's [9] cases (Case VII) had glandular, pulmonary, and uveal signs, together with a lesion of the spinal cord, situated between T 4 and T 12. Ataxia, paraparesis, and impairment of bladder control were present. The patient did not respond to corticotropin (ACTH), 100 mg. daily for 11 days. Seven months later she received a course of cortisone, with initial improvement. The disease subsequently relapsed in spite of continued therapy.

Successful steroid treatment of brain lesions due to sarcoidosis has, however, been reported.[5]

Aszkanazy [1] reported five neurological cases, one of which involved the spinal cord. At autopsy the cord was found to be infiltrated by granulomatous nodules.

Jefferson [6] reported four cases of nervous system sarcoidosis. In one case the spinal cord was diseased, causing permanent paraplegia.

De Morsier, Maurice, and Martin [3] reported two cases, one of which presented the clinical picture of atypical amyotrophic lateral sclerosis, with complete quadriplegia. At autopsy diffuse disease of muscles and also of the brain and cord was found.

All these eight cases, including those treated with cortisone, went on to permanent damage, except the one mentioned by Reisner. This is understandable, since the enclosed space occupied by the cord is small and the cord columns, once destroyed, do not regenerate.

For this reason it seems worth while to report the following case of sarcoidosis with cord involvement which recovered completely with cortisone therapy.

A 24-year old white lawyer was first seen in consultation on July 3, 1952.* He had noticed pain in his calves five months previously, followed by pain in his right hip and lower back. The pain became worse on coughing, sneezing, laughing, and straining. For the last two months he had noticed difficulty in walking a straight line; he could not stand on his toes, climb stairs, walk rapidly, or stand on one leg.

He had to walk with a shuffling gait. One week previously he had developed loss of potentia, difficulty in urination, and dribbling. He was seen by a urologist, who found a normal prostate and 300 cc. of residual urine and diagnosed his urinary condition as a cord bladder. The patient also complained of extreme general exhaustion and weakness.

The past history was not remarkable. He had had frequent upper respiratory infections and had developed premature alopecia several years previously. He slipped once, several months previously, but did not hurt his back. He had had a slight cough for a year which he attributed to cigarettes.

Physical examination revealed a tall cachectic young man who shuffled into the examining room, unable to lift his feet from the floor. His height was 72 in.; weight, 137 lb.; blood pressure, 120/70; pulse, 92. Heart and lungs seemed normal on physical examination. There was no tenderness of the spinal column. A generalized lymphadenopathy, including cervical, axillary, and inguinal nodes, was elicited. The nodes were discrete, only moderately enlarged, and not tender. Liver and spleen could not be palpated, though some resistance in the left upper quadrant was thought to be present. The knee jerks and ankle jerks were absent.

The chest x-ray showed enlarged hilar glands and diffuse pinpoint opacities throughout both lung fields. The gastrointestinal series showed an enlarged spleen indenting the greater curvature of the stomach.

The patient was hospitalized at the Beth-El Hospital. Neurological examination by Dr. H. Agin revealed bilateral hyperalgesia, corresponding to a zone between T 12 and L 2, impaired sensitivity to pin prick and touch over the left saddle-seat area; normal abdominal but depressed cremasteric reflexes, and absent knee jerks and ankle jerks. The Babinsky response was normal.

A spinal tap obtained clear spinal fluid with 4 lymphocytes per cubic millimeter. The protein content was elevated to 128 mg. %, and the sugar content was slightly decreased to 40 mg. %. The chest x-rays and gastrointestinal series confirmed the outside findings. The x-rays of the phalanges were negative. The ECG, the blood cell count,

*At the Department of Medicine, Empire Medical Group, H. I. P.

and the sedimentation rate were normal. The blood chemistry was normal: serum albumin, 3.4 gm. %; globulin, 2.9 gm. %; calcium, 10.2 mg. %; phosphorus, 3.4 mg. %; alkaline phosphatase, 2.4, Bodansky units per 100 cc.; thymol turbidity, 2 units.

An inguinal node was removed for biopsy, and the histologic picture was reported as consistent with sarcoidosis.

The patient was started on daily intravenous injections of corticotropin, 25 mg. dissolved in 500 cc. of 5% dextrose in water, given slowly over a period of eight hours. This was continued for eight consecutive days, ending on Aug. 10. The patient responded dramatically after the third corticotropin injection. The bladder control was promptly restored; he was able to walk normally; the exhaustion disappeared, and he was discharged from the hospital in a much improved condition.

On Sept. 5 all his symptoms and signs returned. He was then treated perorally with cortisone; the first day, 300 mg.; the next 2 days, 200 mg., and for the next 10 days, 150 mg. was given. The daily dose of cortisone was then reduced to 100 mg. Two days later insomnia developed and 75 mg. was given. Two grams of potassium chloride was administered daily. As before, there was an excellent response to steroid therapy which manifested itself already after the first dose as a marked increase in appetite.

On Oct. 1, 1952, the patient had marked polydypsia and polyuria (about 4 qt.). This lasted several months and gradually subsided. The cortisone dosage was reduced to 50 mg. per day.

On Dec. 6, 1952, the patient felt quite well. He volunteered the information that there had been a noticeable growth of hair over the frontal area of his scalp, which had been completely bald before. Chest x-rays showed marked recession, and cortisone was discontinued on Dec. 6, 1952, after three months of administration.

For the next three months without cortisone the patient complained of great fatigue, difficulty in concentration, somnolence requiring 12-16 hours of sleep, pain in the hips, and a persistently clogged nose.

On April 1, 1953, he again developed a generalized lymphadenopathy in the anterior and posterior cervical chains and axillary and inguinal nodes. He also developed a bluish black nodule over the sacrum.

He was hospitalized overnight, and the skin nodule and one lymph node were removed. The skin was reported as normal. The lymph node again showed granulomatous changes consistent with sarcoid. A stain for acid-fast bacteria was negative.

On May 7, 1953, after a five-month lapse, patient was again given cortisone. The dosage was 300 mg. for the first two days, 200 mg. for the next four days, and 150 mg. thereafter. In two weeks the nodes were completely gone and patient felt marked subjective improvement.

On June 7, 1953, cortisone was reduced to 75 mg., and on July 24, 1953, to 50 mg. Knee jerks at that time were 1+. On Sept. 25, 1953, cortisone was reduced to 25 mg., but on Nov. 5, 1953, it had to be increased to 100 mg. per day because of shortness of breath and a marked increase in lung infiltrations on x-ray. The patient promptly improved, and the dose was reduced to 50 mg. on Dec. 5, 1953. In July, 1954, patient had intercourse for the first time since the onset of his illness (two years before) but had no emission.

On Dec. 15, 1954, cortisone was finally stopped after having been administered for two and one-half years. During this period attempts to stop or sharply reduce the daily dose had always been followed by relapses. In March, 1955, the patient had normal intercourse again. This time he had an emission, but the semen analysis showed only clear fluid. In June, 1955, he was able to resume normal sexual activity. In September, 1955, sperm analysis showed 2,140,000 sperm per cubic millimeter. On Jan. 3, 1956, sperm analysis showed 39,500,000 sperm per cubic millimeter. That month, one year after cessation of cortisone, his hair began to fall out again and the scalp reverted to its former baldness. In March, 1956, neurological examination was entirely negative. In May, 1956, chest x-ray became normal for the first time, one and one-half years after stopping cortisone. In October, 1956, his wife became pregnant.

Comment

This young man had widespread sarcoidosis, and the evidence strongly points to involvement of the spinal cord by the same process. The prompt improvement associated with corticotropin therapy, the prompt relapse when it was stopped, and the prompt improvement again with cortisone indicates that steroid therapy is of value in this condition.

960 Sterling Pl. (13).

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The Effect of Treatment on Mortality Rates in Severe Hypertension

A Comparison of Medical and Surgical Regimens

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Introduction

The mortality rates among our patients treated with oral ganglion blocking agent and hydralazine have been here compared with the mortality rates reported in the literature as being associated with other antihypertensive regimens, particularly surgical sympathectomy. The comparison was made difficult by the differing criteria used by various authors in grading the severity of the disease prior to therapy. Because effective antihypertensive drugs have been used for relatively short periods of time, they can be adequately evaluated only in seriously ill patients with significant and predictable mortality rates during the available observation period.

Our series consisted of all the previously untreated nonuremic adult patients who received the combination of ganglion blocking agent and hydralazine before or during August, 1953, under our supervision. The fate of each was considered exactly four years after he began therapy. All patients who began such combined therapy were included in the overall mortality statistics, regardless of whether they continued to take their drugs or not. Our patients were divided on the basis of their pretreatment status into two groups corresponding to Groups 3 and 4 (Smithwick classification), so that they could be compared with Smithwick's own series. In order further to define mortality as a function of the severity of the disease before treatment, Group 4, the larger and more seriously compromised group of our patients, was divided into two subgroups corresponding to the benign and malignant stages of hypertension. Finally, the patients with malignant hypertension were divided again into those with and without azotemia. Prognosis was also considered in relation to race, sex, age, economic status, cooperation, and adequacy of control of blood pressure.

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From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, and Barnes Hospital, St. Louis, under a grant-in-aid from the National Heart Institute, United States Public Health Service, the Ciba Pharmaceutical Products Inc., and the Life Insurance Medical Research Fund. Established Investigator, American Heart Association (Dr. Perry).

Material and Methods

Before therapy the hypertensive cardiovascular disease of every patient included in this study was carefully classified according to Smithwick's[1] and Keith, Wagener, and Barker's[2] criteria. Each had a Smithwick numerical grade of 4 or more and therefore belonged in either Group 3 or 4 (Smithwick classification).* No patient was denied

* According to Smithwick's system of grading, patients are given one point each for cerebrovascular accident without residual, abnormal electrocardiogram, cardiomegaly, impending cardiac failure, or slight diminution in renal excretory function. They are given two points each for angina pectoris, residual of a cerebrovascular accident, frank cardiac failure, unsatisfactory fall in blood pressure following sedation, or moderate diminution in renal excretory function. They are given three points for marked diminution in renal excretory function. They are given four points for abnormal nitrogen retention. Patients are placed in Groups 3 and 4 (Smithwick classification) if they have a numerical grade of 4 or more points. Those assigned to Group 4 (Smithwick classifica-

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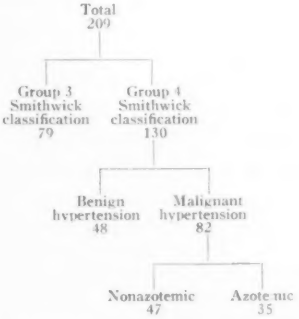
therapy because of the severity of his disease. Excluding 23 persons who had been surgically sympathectomized previously, 6 others with more than 100 mg. of nonprotein nitrogen per 100 ml. plasma before therapy, and a child of 6 years,† there remained a total of 209 untreated nonuremic adult patients who began to receive oral hexamethonium chloride and hydralazine hydrochloride under our supervision during the two years beginning in August, 1951, and ending with August, 1953. Their ages ranged from 27 to 70 years, with a mean of 49 years. Included were 23 Negroes, 94 men, and 49 ward patients; the average age for the three categories was 42, 50, and 44 years, respectively.

Of our 209 patients, 79 were classified as belonging to Group 3 and 130, to Group 4 (Smithwick classification).[3] Of the one hundred thirty patients in Group 4, eighty-two were considered to have malignant stages of hypertension.‡ All 82 had papilledema and, hence, Keith, Wagener, and Barker Grade IV ocular fundi; in 77 hemorrhagic and exudative retinitis were observed, while 3 had only hemorrhages and 2 had only exudates. Each of the 82 had a mean supine diastolic pressure of at least 120 mm. Hg at hospital rest; 78 had mean pressures over 130 mm. Hg, the average number of determinations before treatment being 17 per patient. The entire 82 had proteinuria. Although 47 patients had no abnormal retention of nitrogen, none was able to excrete more than 22% of 6 mg. of intravenously injected phenol red within 15 minutes, and only five excreted more than 15%. The remaining 35 patients had azotemia without evident cardiac failure or any of the common signs of uremia. Their pretreatment levels of circulating nonprotein nitrogen varied from 31 to 78 mg. per 100 ml. of plasma (25 mg. of nonprotein nitrogen per 100 ml. of plasma was the upper limit of normal for the method used). The foregoing division of patients into groups is summarized below, and the number of patients in each category is indicated.



Therapy with oral hexamethonium chloride and hydralazine hydrochloride was instituted in the previously described manner.[8] The regimen involved an invariant dose of hydralazine plus a variable dose of ganglion blocking agent five or six times a day, with the dose of the latter dependent on the level of systolic pressure.§ The mean

tion) have, in addition to four points, one of the following: a resting diastolic pressure of at least 140 mm. Hg, residual of a cerebrovascular accident, frank cardiac failure, or a combination of unsatisfactory response to sedation and inability to excrete 15% of intravenously injected phenol red in 15 minutes. This method obviously assesses cardiovascular and renal damage resulting both from the hypertensive process and the associated atherosclerosis.

† When we first saw them at different intervals after varyingly complete sympathectomies, 9 patients who belonged to Group 3 (Smithwick classification) and 14 who belonged to Group 4 were treated with ganglionic blockade and hydralazine because of severe persistent or recrudescent hypertension; 7 from Group 3 and 10 from Group 4 were alive after four years of drug therapy. The six uremic patients with malignant stages of hypertension all died within a month of entering the hospital; recently we have seen three similar patients whose blood pressures have been lowered with improvement of renal function and temporary rehabilitation. The child who was excluded from the series belonged to Group 4 (Smithwick classification); despite chronic bilateral pyelonephritis, she is alive and apparently developing normally after five and one-half years of medical sympathectomy plus hydralazine administration, although her mean diastolic pressure remains consistently over 100 mm. Hg. A few patients previously mentioned[1] are not included because we were not actually responsible for therapy, although we were consulted.

‡ There were 48 patients without papilledema who were not considered to have malignant stages of hypertension, although they belonged to Group 4 (Smithwick classification); five of them had significant hemorrhagic and exudative retinitis. When therapy was instituted, 16 were in frank heart failure, 12 had obvious residua from vascular accidents, and 20 neither excreted phenol red well nor had an adequate antihypertensive response to sedation.

§ Antihypertensive therapy was instituted with 125 mg. of hexamethonium chloride every four hours unless the systolic pressure, which was measured just before each dose with the patient in the supine position, was less than 140 mm. Hg. The initial 125 mg. dose of hexamethonium was doubled on the second day, tripled on the third, and so on. Half doses were given for pressures between 130

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diastolic pressure was calculated for every patient during the final 72 hours of hospitalization; all mean pressures were the average of 18 individual determinations, each of which was measured 4 hours after antihypertensive medication, with the patient in the supine position. An effort was made to follow every patient for four years, but nothing that happened to him thereafter was considered in this study. Particular attention was paid to how long each survived and whether he continued to take ganglion blocking agent and hydralazine as instructed.

Results

Of our 79 patients treated with oral ganglion blocking agent and hydralazine, who were classified as belonging to Group 3 (Smithwick classification), 69 are known to have been alive four years after beginning treatment with drugs; 8 are known to have died within four years of starting therapy, and the fate of 2 is unknown. The left hand side of Figure 1 compares the 10% mortality of our 77 followed patients with the mortality of similarly severe hypertensive patients belonging to Group 3 and reported by Smithwick. The corresponding four-year mortality of 115 surgically sympathectomized patients was 19% and of 59 untreated patients was 58%.[4]

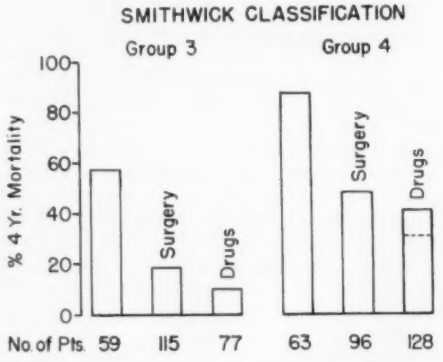

Fig. 1.—Four-year mortality for three series of hypertensive patients belonging to Groups 3 and 4 (Smithwick classification). Above each bar of the graph is an indication of therapy when any was administered. In Group 4, the untreated and drug-treated series were consecutively taken and included azotemic patients, whereas azotemic patients were excluded from the surgically sympathectomized series. To make the drug-treated series comparable to the surgically sympathectomized series a dotted line has been drawn to indicate the 33% four-year mortality for the 93 drug-treated patients who were not azotemic. If only *cooperative* drug-treated patients were considered the 4-year mortality rate in Group 3 fell from 10% to 7% and in Group 4, from 33% to 23%.

Of our 130 more severely compromised patients who belonged to Group 4 (Smithwick classification), 81 are known to have been alive after four years of drug therapy and 47 are known to have died during this interval. The right-hand side of Figure 1 compares the 43% mortality of our 128 followed patients with the mortality of patients belonging to Group 4 and reported by Smithwick. The corresponding four-year mortality of 96 surgically sympathectomized patients was 48% and of 62 untreated patients was 87%.[4] Since none of the surgically treated patients was azotemic, the Figure also indicates the 33% mortality of the 93 nonazotemic patients treated with drugs. Furthermore, as mentioned in the legend, the 33% mortality is decreased to 23% if the relatively few patients who discontinued drug therapy against advice are excluded from the calculations.

Of our 82 patients belonging to Group 4 (Smithwick classification) who also had malignant stages of hypertension with

and 140 mm. Hg and quarter doses, for pressures between 120 and 130 mm. Hg. The dose of hexamethonium was increased until the average supine systolic pressure approached 140 mm. Hg. An invariant dose of oral hydralazine hydrochloride was then begun. The initial dose of 25 mg. every four hours was doubled on the second day, tripled on the third, and so on. The optimal dosage of hydralazine was considered to be the dose which gave the most even control of blood pressure and usually approximated one-fifth of the maximal dose of hexamethonium. When the best tolerable regimen had been found, the patient was ambulated; he was no longer wakened at night for medication, and he was taught to gauge his drug requirement with a sphygmomanometer. Unlike many subsequently treated patients, the 209 considered here had their dose of blocking agent governed by their supine systolic pressure in the hospital but by their sitting pressure at home. After four years of therapy postural hypotension was ordinarily unimportant, and the sitting pressure approximated the supine pressure. Hexamethonium was usually replaced with other ganglion blocking agents as they became available.

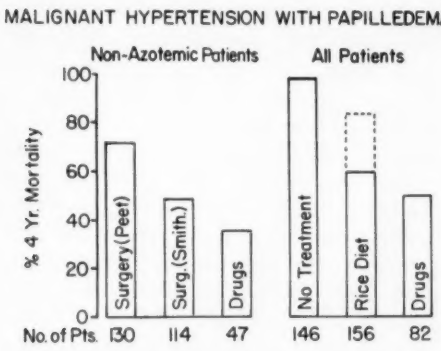

Fig. 2.—Four-year mortality for several series of differently treated patients with malignant hypertension manifested by papilledema. On the left, nonazotemic drug-treated patients were compared with nonazotemic patients sympathectomized by a supradiaphragmatic procedure[6] and by a thoracolumbar procedure.[1] On the right, consecutive series of untreated and drug-treated patients, including azotemic patients, were compared as well as possible with similar patients who received rice-and-fruit diets. Since complete data were not available for the latter, maximum and minimum values are indicated. If only cooperative drug-treated patients were considered, the four-year mortality was less than 40% even with azotemic patients included.

papilledema, 41 are known to have been alive and 41 to have been dead four years after beginning ganglionic blockade and hydralazine. Of the 47 who were not azotemic when therapy began, only 17 died within four years. Because surgical series generally excluded azotemic patients, the left-hand side of Figure 2 compares the 36% mortality of our 47 nonazotemic but malignant hypertensive patients with the mortality of two series of apparently similarly chosen hypertensive patients who were surgically sympathectomized. The four-year mortality was 72% for the first series, which consisted of 130 patients on whom Peet and Isberg had performed supradiaphragmatic sympathectomies (13 azotemic patients were excluded from the calculations).[6] The four-year mortality was 48% for the second series, which consisted of 114 patients on whom Smithwick had performed thoracolumbar sympathectomies.[1] The right-hand side of Figure 2 compares the 50% mortality of our entire group of 82 azotemic and nonazotemic malignant hypertensive patients with the mortality of two series of comparable patients. The four-year mortality was 98% for the first series, which consisted of 146 untreated patients followed by Keith, Wagener, and Barker.[2] The four-year mortality was between 60% and 83% for the second series, which consisted of 156 patients who were given rice-and-fruit diets by Newborg and Kempner.[5]

In Table 1 the relationships of prognosis to cooperation by the patient and control of blood pressure are emphasized. Of 205 followed patients, 27 discontinued and 178 continued treatment; their respective mortalities during the four years following in-

TABLE 1.—*Analysis of 209 Patients Treated by Ganglionic Blockade and Hydralazine* *

		Total	Followed		Continued		Controlled	
	Total	Lost	Followed	Discontinued	Continued	Uncontrolled	Controlled	Died in Yr	Lived Yr
Total	209	4	205	27	178	42	136	13	123
			(31)	(78)	(24)	(45)	(17)		(8)
Group 3	79	2	77	9	68	11	57	0	57
			(10)	(33)	(7)	(27)	(4)		(4)
Group 4	130	2	128	18	110	31	79	13	66
			(43)	(100)	(34)	(52)	(27)		(12)
Group 4 benign	48	2	46	4	42	11	31	3	28
			(30)	(100)	(24)	(36)	(19)		(11)
Malignant nonazotemic	47	0	47	9	38	9	29	3	26
			(36)	(100)	(21)	(33)	(17)		(8)
Malignant azotemic	35	0	35	5	30	11	19	7	12
			(69)	(100)	(63)	(82)	(53)		(25)

* Upper figures indicate the total number of patients in each category and figures in parentheses indicate four-year mortality in per cent

ception of drug therapy were 78% and 24%.‖ Of the 178 cooperative patients, 42 had mean diastolic pressures of 100 mm. Hg or more just before leaving the hospital and 136 had lower values; their respective mortalities were 45% and 17%.¶ Of the 136 patients whose blood pressures were considered adequately controlled, 13 died during the first year of treatment and 10 died in the next three years. The Table breaks down the over-all results to show the differences between Groups 3 and 4 (Smithwick classification); moreover, it further divides Group 4 into three mutually exclusive subgroups of patients with increasingly severe disease prior to treatment.

In Table 2 the relationship of prognosis to race, sex, age, and economic status is considered but only for our 128 followed patients who belonged to Group 4 (Smithwick classification). The 76% four-year mortality of the small number of Negro patients was in sharp contrast to the 38% mortality for the non-Negroes. On the other hand, the 50% to 53% mortality for male, old, and ward patients was not markedly different from the 37% to 39% mortality for female, young, and private patients. The Table not only gives the results for all patients belonging to Group 4 but also for the subgroup of patients with malignant stages of hypertension and for the still smaller number of malignant hypertensive patients with azotemia.

Death was apparently due to renal failure in 30 of the 55 known fatalities and was probably related to the cardiovascular disease in 12 others. Five Negroes and three others died of nonuremic *fibrinous pneumonitis*,[7] an entity which at one time complicated hexamethonium therapy but which has recently become vanishingly rare. Two patients developed fatal neoplasia, and the cause of death is unknown for the remaining three cases. Nineteen patients developed symptoms of toxicity from hydralazine,[8] requiring discontinuation of the drug; none died directly as the result of such toxicity, but two succumbed to recrudescent hypertension and its sequelae.

Comment

The foregoing comparisons of therapeutic regimens are subject to valid objections. The most serious problem is that of obtaining comparable and homogeneous series of patients. Criteria for grading the severity of hypertensive cardiovascular disease differ greatly, and such criteria are often partially subjective. Moreover, the populations so defined are somewhat heterogeneous even at best. Nonetheless, when the severity of the hypertensive process has been the basis

‖ In addition to the 27 patients who abruptly discontinued ganglionic blockade against advice because of side-effects, 13 of the 209 patients considered in this paper discontinued ganglionic blockade gradually and under our direction after more than a year of therapy. Their well-controlled blood pressures had resulted in an automatically decreased intake of blocking agent. Eight were from Group 3 (Smithwick classification), and five, from Group 4. One of these patients with malignant hypertension died with a myocardial infarction 46 months after starting treatment. Another from Group 4 died at 43 months with a cerebral thrombosis, of which she had had several before drugs were begun. The remaining 11 are asymptomatic and working full-time with normal blood pressures. Eight have been able to discontinue hydralazine as well without compromising their diastolic normotension (Circulation 8:528, 1956).

¶ The percentage of the living patients with mean supine diastolic pressures below 100 mm. Hg gradually fell from 76 at the time of hospital discharge to 71 following four years of ganglionic blockade and hydralazine. After four years of therapy, 96 of the 113 living patients who initially had mean diastolic pressures below 100 mm. Hg continued similarly well controlled. Two opposing trends influenced the percentage of treated patients whose blood pressures were controlled at any given time: first, patients with the highest mean pressures died early, and second, some patients with initially well-controlled diastolic pressures tended to *escape* from control. In contrast, Evelyn et al. reported that about 10 days after the second stage of lumbodorsal sympathectomy almost half of 114 patients had mean supine diastolic pressures over 100 mm. Hg. Five years after a similar surgical procedure only 8 of 100 different patients had "normal" blood pressures, and only 13 more had "significantly reduced" blood pressures (J. A. M. A. 140:592, 1949).

TABLE 2.—*Analysis of 128 Drug-Treated Patients Belonging to Group 4 (Smithwick Classification) and Having Four-Year Follow-Up* *

		Race		Sex		Age		Status	
	Total	White	Negro	Female	Male	<50 yr.	>50 yr.	Private	Ward
Group 4	128	111	17	70	58	80	48	88	40
	(42)	(38)	(76)	(37)	(50)	(39)	(50)	(39)	(53)
Malignant	82	65	17	43	39	58	24	47	35
	(50)	(43)	(76)	(47)	(54)	(48)	(54)	(45)	(57)
Azotemic	35	26	9	19	16	23	12	15	20
	(69)	(65)	(78)	(58)	(81)	(65)	(75)	(67)	(70)

* Upper figures indicate the total number of patients in each category and figures in parentheses indicate four-year mortality in per cent. Patients discontinuing therapy are included.

of selection, there has often been good agreement between authors. Thus, Keith, Wagener, and Barker found 5.4 months to be the median and 10.5 months, the mean survival time after the discovery of hypertensive papilledema,[2] while Palmer, Loofbourow, and Doering obtained a value of 4.0 months for the former[9] and Schottstaedt and Sokolow obtained a value of 8.4 months for the latter.[10]

In the comparison of antihypertensive drugs and surgical sympathectomy cited above, the pretreatment renal status of Smithwick's own sympathectomized patients who had Keith, Wagener, and Barker Grade IV fundi was demonstrably better than the renal status of our nonazotemic drug-treated patients with malignant stages of hypertension. Nearly half of Smithwick's patients excreted 25% of intravenously injected phenol red in 15 minutes,[1] of hypertension. Nearly half of Smithwick's patients excreted 25% of intravenously injected phenol red in 15 minutes,[1] whereas none of our patients was able to do so. In addition, the percentage of Negroes, with their apparently poorer prognosis, was presumably higher among our drug-treated patients. Such differences must be weighed when the benefits of therapy are compared. Most series of surgically sympathectomized patients with severe hypertension were purposely selected in various ways to avoid certain groups with high operative mortalities. For instance, Hammarstrom and Bechgaard included no one with myocardial infarction or auricular fibrillation and only a few with renal insufficiency or cardiac decompensation.[11] Woods and Peet excluded persons over 60 and most of those over 50 years of age, as well as anyone with either cardiac or renal decompensation.[12] We excluded no one for such reasons.

Difficulties of comparison naturally increase if the basis of selection is broadened to include the severity of the atherosclerotic as well as the hypertensive process, as is done in Smithwick's and several other schemes of classification. Both a resting diastolic pressure over 140 mm. Hg and less hypertension coupled with cardiac failure or cerebrovascular accident are ominous, but they suggest dissimilar outcomes and certainly need not imply the same life expectancy.

As yet there are no published long-term mortality statistics for malignant hypertensive patients following the relatively new procedure of total or subtotal adrenalectomy combined with lumbar sympathectomy. The four-year mortality for 52 such patients belonging to Group 4 (Smithwick classification) apparently was between 40% and 50%,[13,14] which is probably not significantly different from the mortality following surgical sympathectomy alone.

There are several preliminary reports on the effect of ganglionic blockade without hydralazine. McMichael and Murphy found that 34% of 32 patients with hypertension characterized as "malignant" survived three years of parenteral methonium therapy.[15] Their results, like ours, were

prejudiced by the pulmonary disease which followed the use of hexamethonium. Likewise, Smirk apparently found that 47% of 19 patients with "maligant" hypertension lived for more than two years after institution of oral methonium therapy.[16] More recently, McMichael and Smirk have both mentioned better than 50% four-year survival in selected groups of "malignant" hypertensive patients treated with ganglion blocking agents and rauwolfia alkaloids.[17] Moyer, who has used the same combination, reported a two-year survival for 8 of 11 nonazotemic and 9 of 15 azotemic "malignant" hypertensive patients.[18]

Obviously the over-all mortality in any group of medically treated patients is improved when the patients who discontinued therapy against advice are excluded from the calculations. By omitting our uncooperative drug-treated patients the four-year mortality rate was lowered from 10% to 7% for Group 3 (Smithwick classification) and from 36% to 21% for nonazotemic malignant hypertensive patients. These figures are less than half of the comparable mortality rates for Smithwick surgically sympathectomized patients. Cooperation is, of course, an individual matter between patient and physician and will vary widely; little is required after surgery has once been performed.

Conclusions

During the four years following the institution of therapy, the mortality was lower in our series of patients treated with a combination of ganglionic blockade and hydralazine than it was in Smithwick's reported series of surgically sympathectomized patients. If the severity of the cardiovascular disease was graded on the basis of both hypertensive and atherosclerotic processes (Smithwick classification), medical and surgical mortalities after four years were 43% and 48%, respectively, for patients belonging to Group 4, the most severely compromised group. If the grading was based only on the hypertensive process (Keith, Wagener, and Barker classification), the medical and surgical mortalities were 36% and 48%, respectively, for nonazotemic malignant hypertensive patients. By excluding the one patient in eight who discontinued therapy, the medical mortality of 36% was decreased to 21%. For all groups of nonazotemic patients who survived the first year of drug therapy with adequately controlled diastolic pressure, the mortality approximated 10% during the next three years. Drug therapy was about half as effective for Negro as for white patients; however, sex, age, and economic status were not of such marked prognostic significance.

Summary

The fate of 209 patients having Smithwick numerical grades of 4 or more points and begun on ganglion blocking agent and hydralazine by us four or more years ago is considered. The four-year mortality of our followed patients, including those who discontinued therapy, ranged from 10% among patients belonging to Group 3 (Smithwick classification) to 69% among patients with malignant stages of hypertension complicated by azotemia. The 50% mortality for all drug-treated patients during the four years after discovery of malignant hypertension was found to compare favorably with reported mortalities for untreated patients, patients given rice-and-fruit diets, and surgically sympathectomized patients after allowance had been made for exclusion of azotemic patients from the surgical series. In the drug-treated series an increasingly good prognosis was found for the successively smaller subgroups of patients who continued therapy, whose blood pressure was initially controlled by drugs and finally who survived a year of treatment. Mortality was related to race but relatively independent of sex, age, and economic status.

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Addendum

Since this paper was prepared, Smirk has discussed the results of drug therapy in severe hypertension. He has reported that 56% of his malignant hypertensive patients treated with ganglionic blockage have survived four years (Smirk, F. H.: High Arterial Pressure, Springfield, Ill., Charles C Thomas, Publisher, 1957).

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The Hepatojugular Reflux

Influence of Magnitude of Force Applied to Hepatic Area on Venous Pressure in Subjects With and Without Chronic Congestive Heart Failure

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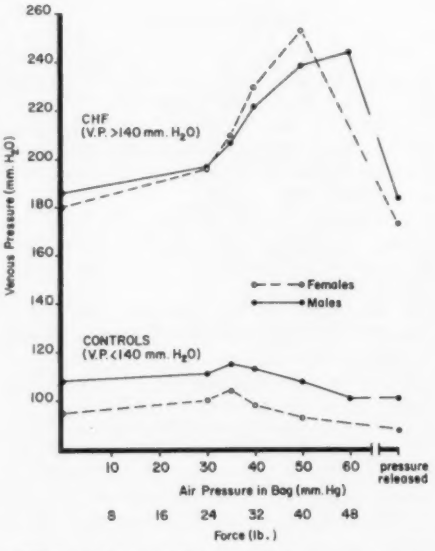
The hepatojugularometer was devised to permit determination of the amount of force applied over the hepatic area to elicit the hepatojugular reflux and to allow this force to be varied as desired.[1] The degrees of response to this test among different persons and at different times in the same person cannot be compared accurately unless at least the force applied to the hepatic area is known.[1] This problem was further investigated by studying the responses of a series of subjects with and without chronic congestive heart failure.

Materials and Methods

The hepatojugularometer was employed, as described previously,[1] in 273 adult subjects: 138 men and 72 women without chronic congestive heart failure or edematous states and 42 men and 21 women with failure. All control subjects had a venous pressure below 140 mm. H_2O, and all patients with congestive heart failure, above this level. While a known force was applied with both hands to the rubber bag resting over the hepatic area, the pressure was recorded in the median basilic vein with the phlebomanometer.[2] Venous pressure was recorded first without application of any force to the rubber bag and then, consecutively, with forces sufficient to raise the air pressure within the bag to 30, 35, 40, 50, and 60 mm. Hg. of pressure.

Results

Control Subjects.—Results are summarized by the Figure. The venous pressure in the subjects without congestive failure rose 4 mm. H_2O when the pressure in the rubber bag was 30 mm. Hg (24 lb. of force) and another 4 mm. H_2O when the pressure in the bag was raised to 35 mm. Hg pressure (about 28 lb. of force). As the force over the liver was further increased to about 48 lb., the pressure in the median basilic vein progressively declined (Figure), the mean change for all 210 subjects being a decline of about 8 mm. H_2O. The direction and degree of change was fairly consistent from subject to subject. The hepatojugular reflux did not differ remarkably for men and for women. The women, in general, were not able to with-



Effect of force applied to hepatic area on venous pressure in subjects with and without chronic congestive heart failure.

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stand readily a force of about 60 lb. over the hepatic region.

Patients with Congestive Heart Failure. The responses of the patients with congestive heart failure to the same force applied successively to the hepatic area varied. All had venous hypertension initially, and in all the pressure in the median basilic vein rose remarkably as the force applied to the hepatic area was increased from 0 to about 48 lb. (Figure). When the force was raised from 40 to 48 lb., the venous pressure changed less than for the other incremental changes in force; it either rose less abruptly or declined slightly. No difference in response by sex was observed, except that the women were not able to tolerate readily a force of 49 lb.

Comment

These studies show the dependence of the magnitude of change in venous pressure upon the force applied to the hepatic region. This force must obviously be known if resultant effects on venous pressure are to be accurately compared. The mere statement of change in venous pressure to application of unknown amount of force to the hepatic region is not sufficient. The hepatojugular reflux curves for the subjects with and without congestive heart failure (Figure) differ strikingly and may be used reliably to differentiate the presence or absence of congestive failure in a patient.

If only a single force is to be applied, one sufficient to produce a pressure of 40 mm. Hg in the rubber bag of the hepatojugolarometer appears to be most effective for clinical detection of congestive heart failure.

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Second Field Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine

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Earlier reports [1-5] from this laboratory described the development and evaluation in the field of a formalin-killed bivalent adenovirus [6-8] vaccine of monkey-kidney origin. The vaccine was prepared at the Walter Reed Army Institute of Research, and the evaluation consisted of a controlled field study conducted during the winter of 1956 in 624 newly inducted recruits at Fort Dix, N. J. The vaccine was highly effective, commencing one week after vaccination, and produced a 98% reduction in amount of adenovirus-caused respiratory illness. During the winter of 1957, a second controlled field evaluation of the vaccine was carried out among 8238 recruits stationed at Fort Leonard Wood, Mo. The vaccine employed in this trial was provided by Lederle Laboratories and was prepared under commercial conditions. This paper presents the findings in the field trial at Fort Leonard Wood, compares the potency values of the Lederle and Walter Reed vaccines, and presents data concerning the reliability of the complement-fixation (CF) and virus-recovery techniques for specific diagnosis in the laboratory of adenovirus-caused respiratory illness among vaccinated and non-vaccinated persons.

Methods

Field Study.—Study Population: The field evaluation was carried out at Fort Leonard Wood, Mo., during January-May, 1957. The post strength at the time was approximately 20,000, but the study was confined to 43 companies of the Second and Third Basic Training Regiments and the training regiment of the Reserve Forces Act. These companies were formed during January-March from new inductees, and each consisted of slightly more than 200 men. Details of the composition of Fort Leonard Wood and of the adenovirus respiratory disease problem there have been presented in earlier reports.[9]

Study Plan: Within 30 hours of arrival on post, each recruit was given a single 1.5 ml. injection intramuscularly of adenovirus vaccine or of formalin-saline placebo (1:8000 formalin with 0.002% phenol red). Persons with army serial numbers ending in 3, 6, or 9 received the adenovirus vaccine, and those remaining were given placebo. During the study, approximately 14,000 persons were given injections, but, of these, only 8238 remained on post and comprised the study group. The remaining men were transferred off post for training elsewhere or were lost from the study for other reason.

The personnel in the study were observed during the period from vaccination until completion of their eight weeks of basic training. The evaluation of vaccine was based on comparison in the vaccinated and placebo control groups of the admissions to the hospital for acute respiratory illness which occurred more than seven days after injection. None of the recruits knew whether he had received vaccine or placebo. Reporting for sick call by the recruits was based on individual initiative, and the decision whether to admit to the hospital or to treat on an outpatient basis was made by the medical staff. These officers did not know the vaccination status of the men and were only remotely aware of the study and its purpose. The general criteria for hospital admission for respiratory illness during the study were temperature of 100.4 F or higher and the clinical impres-

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From the Department of Respiratory Diseases, Walter Reed Army Institute of Research.

sion that the patient was suffering with an acute respiratory disease. Notification of the hospital admission of persons in the study group was obtained by observation of the daily hospital admission and discharge record, which listed patients by name, company, and diagnosis. The recording of respiratory illness in each person was based on the final clinical diagnosis upon discharge from the hospital. The records of the study were so handled that each person was followed by name and by company from the time of arrival on post to the end of the basic training period.

Collection of Clinical Specimens for Laboratory Testing: Throat washings and acute and convalescent blood specimens were collected at random from a representative sample of the cases for purpose of establishing the specific diagnosis and the type of infecting virus. Throat washings for virus recovery were collected in nutrient broth from the patients at the time of their admission to the hospital and were stored frozen in sealed containers in solid carbondioxide (Dry Ice) for periods up to five months before testing. Acute-phase blood specimens were taken from the patients at time of admission, and the convalescent specimens were taken 18 to 20 days later. The sera were removed from the clotted blood samples and maintained frozen at —20 C.

Laboratory Study.—Vaccine Production: The bivalent Types 4 and 7 adenovirus vaccine employed in the study was prepared under commercial conditions at the Lederle Laboratories by Dr. Victor Cabasso and staff. The vaccine was produced and tested, with minor modification, by the same general method used to prepare the first lots of vaccine in this laboratory.[1-6] The monkeys employed in the safety test for poliovirus were treated with cortisone according to the regulations.[10] The infectivity titers of the Types 4 and 7 components prior to inactivation were each 10^{-8}, and the CF antigen titers were both 1:4. The total and protein nitrogen values of the Type 4 component were 0.170 and 0.010 mg. per milliliter, respectively, and for the Type 7 component, 0.174 and 0.005 mg/ml. Guinea pig potency assays were performed by the method described earlier,[1-3] and the findings are presented in the body of this report together with the antibody response in human subjects.

Laboratory Diagnostic Tests: Attempts to recover adenovirus from throat washings were made by cultivation in tissue cultures of HeLa cells with use of standard procedures used in this laboratory.[6] Ginsberg's maintenance solution[11] was employed for maintaining the cells, and all cultures were passed three to six times before being discarded as negative. Identification of the adenovirus isolates was made by demonstration of adenovirus group CF antigen,[12] and virus typing was carried out with monotypic rabbit antisera with use of methods used earlier.[6] The serum specimens from the patients were titrated for adenovirus CF antibody content by the standard procedure already described,[6] with use of Type 4 virus (R1-67) CF antigen grown in HeLa cells. A fourfold or greater increase in antibody was considered diagnostic. The serodiagnostic tests for influenza A′ and B were carried out by the standard procedure,[13] with use of the A′-FLW-152 and B-IB1-50 strains. There was little difficulty in interpreting the results of the adenovirus CF tests, even in vaccinated persons. A CF antibody response to the vaccine occurred in only a portion of the vaccinated persons, and the titer usually did not exceed 1:10. Further, adenovirus-caused respiratory illness is relatively infrequent among recruits during the first two weeks on post, allowing time for any response to vaccine to achieve the maximum level and to stabilize before the epidemic occurrence of the disease. In analyzing the tests, the few cases in which respiratory illness with CF titer rise occurred during the early postvaccination period were counted as positive. The consequence of this was a slight tendency to overrate the occurrence of adenovirus cases among vaccinated persons, resulting in a more conservative estimate of the effectiveness of the vaccine. Interpretation of the diagnostic tests for influenza were difficult. Vaccine was given routinely to all recruits shortly after arrival on post, and all titer rises which occurred in the patients within two weeks post vaccination were discarded as negative and due to vaccine. This necessarily gave a false low estimate of influenza incidence on post, though the reduction was probably not great and in no way influenced the adenovirus determination.

Results

Comparison of Immunizing Potency of Lederle and Walter Reed Vaccines in Guinea Pigs and Man.—There is presently no satisfactory quantitative assay method for comparing potencies of adenovirus vaccines. The guinea pig potency test[1-3] employing a single intramuscular injection of vaccine does provide, however, a crude measure of vaccine potency. Table 1 shows that the neutralizing antibody titer of pooled aliquots of sera from guinea pigs given the currently used Lederle vaccine was 1:1 against Type 4 adenovirus and 1:4 against Type 7 virus. In simultaneous tests of the Walter Reed vaccine employed previously,

TABLE 1.—*Comparative Findings in Guinea Pig Potency Tests of Lederle and Walter Reed Bivalent Adenovirus Vaccines*

Vaccine	Neutralizing Antibody Titer * Against Adenovirus	
	Type 4	Type 7
Lederle (current trial)	1:1	1:4
Walter Reed (Fort Dix trial, 1956)	1:4	1:1

* Aliquot pool of sera from 6 vaccinated guinea pigs.

TABLE 2.—*Comparison of Mean Neutralizing Antibody Response in Man to Lederle and Walter Reed Bivalent Adenovirus Vaccines*

Vaccine	Mean Neutralizing Antibody Titer Against Adenovirus		
	Type 4	Type 7	Type 3
Lederle * (current trial)			
Prevacc.	1:1.3	1:4.2	1:1.6
Postvacc.	1:10.7	1:95.9	1:12.0
Walter Reed † (Fort Dix trial, 1956)			
Prevacc.	1:1.6	1:1.4	1:2.3
Postvacc.	1:11.3	1:15.9	1:15.9

* Mean, 12 volunteers.
† 19 volunteers.

the titer was 1:4 against Type 4 and 1:1 against Type 7 virus. In spite of the apparent low titer values, both vaccines were highly effective in preventing adenovirus-caused respiratory illness in human beings, the current Lederle vaccine evaluation being in a predominantly Type 4 epidemic and the Walter Reed vaccine evaluation in an epidemic caused by Type 4 and Type 7 viruses in roughly equal proportions.[1,3,4]

Both the Lederle and the Walter Reed vaccines induced a striking neutralizing antibody response on injection into human volunteers in a single 1 ml. intramuscular dose. Table 2 shows that the mean postvaccination neutralizing antibody titers against Type 4 virus in persons given undiluted Lederle or Walter Reed vaccines were essentially the same, irrespective of the difference shown in the guinea pig assays. The response against the Type 7 virus was the greatest for the Lederle vaccine, but this was probably related, in part, to the higher mean titer of the prevaccination

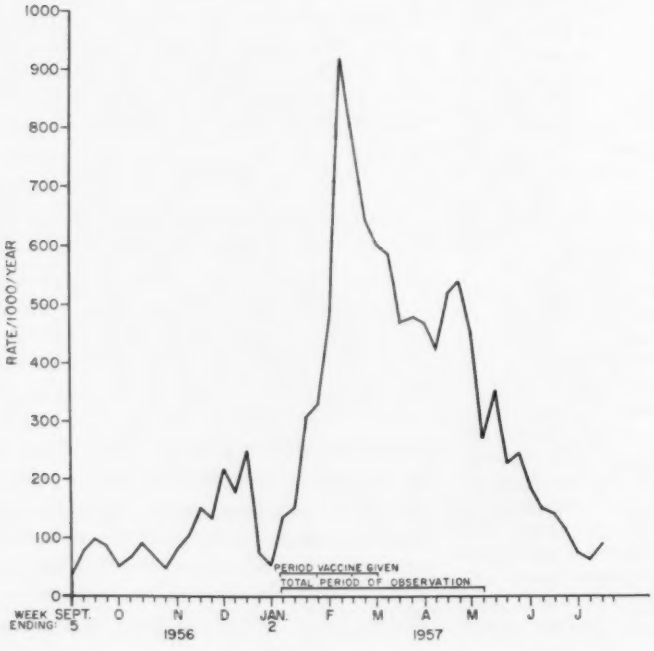

Fig. 1.—Hospital admission rates, "total respiratory disease," Fort Leonard Wood, Mo., showing period when vaccine evaluation program vaccine.

TABLE 3.—*Evaluation of Bivalent Types 4 and 7 Adenovirus Vaccine According to Attack Rate for Total Respiratory Illness, All Causes, and for Adenovirus Cases Only**

		Effectiveness of Vaccine Against												
		Respiratory Illness, According to Adenovirus Diagnosis												
		Respiratory Illness, All Causes				Adenovirus CF Test Results	Computed Adenovirus Cases					Computed Non-adenovirus Cases		
Date Injected	No. in Group	Cases, No.	Attack Rate, %	Ratio Vacc/ Cont.	Reduction in Expected Cases, %	No. Pos./ No. Test.	Pos., %	Cases, No.	Attack Rate	Ratio Vacc/ Cont.	Reduct. in Expected Cases, %	Cases, No.	Attack Rate, %	Ratio Vacc/ Cont.
Summary, Total Period														
1/6–3/7														
Vaccine	2,471	271	11.0			24/161	14.9	40	1.6			231	9.3	
Placebo	5,767	1,370	23.8	1:2.2	55	440/631	69.7	955	16.6	1:10.4	90	415	7.2	1.3:1
According to Vaccination Period														
1/6–1/26														
Vaccine	862	113	13.1			14/84	16.7	19	2.2			94	10.9	
Placebo	1,996	534	26.8	1:2.0	50	162/252	64.3	343	17.2	1:7.8	89	191	9.6	1.1:1
1/27–2/16														
Vaccine	782	82	10.5			7/42	16.7	14	1.8			68	8.7	
Placebo	1,792	426	23.8	1:2.3	57	136/179	76.0	324	18.1	1:10.1	90	102	5.7	1.5:1
2/17–3/7														
Vaccine	827	76	9.2			3/35	8.6	7	0.8			69	8.3	
Placebo	1,979	410	20.7	1:2.3	57	142/200	71.0	291	14.7	1:18.4	95	119	6.0	1.4:1

*Only those cases which occurred 8 or more days post injection are included. During the first 7 days, 24 cases occurred among the vaccinated and 51, among the controls.

sera. The similarity of the mean fold rises against Type 7 virus for the Lederle and Walter Reed vaccines, twenty-threefold and elevenfold, respectively, served to deemphasize the difference in postvaccination mean titers. The antibody response against Heterotype 3 virus was roughly the same for the two vaccines.

Effectiveness of Lederle Adenovirus Vaccine in Preventing Acute Respiratory Illness.—The incidence, week by week, of admissions to the hospital for respiratory illness, all causes (includes cases classed as common respiratory disease, influenza, and pneumonia), from the week ending Sept. 5, 1956, through July 17, 1957, is presented in Figure 1, which shows, also, the period when vaccine was given and the period of observation for occurrence of acute respiratory illness among persons in the study group. The epidemic of acute respiratory illness at Fort Leonard Wood began during November and reached a rate of 250 during December before declining as a result of cessation of induction of troops during the holiday season. The epidemic began again in January, with the introduction of new recruits on post and, after three weeks at relatively low level, rapidly increased to a maximum case rate of 917 during the week ending Feb. 13. The epidemic continued with high rates through May 9, when the study was terminated. The injections of vaccine or placebo were given from Jan. 6 through March 7, a period which started at the beginning of the epidemic and continued through the time of highest incidence of cases in the outbreak. Laboratory diagnostic studies showed that most of the cases which occurred after the third week of January were caused by adenovirus, while most of the cases which were hospitalized earlier in the month were of other etiology.

Table 3 and Figure 2 present a detailed summary of the evaluation of the vaccine at Fort Leonard Wood. It was shown previously [1-5] that the vaccine became effective

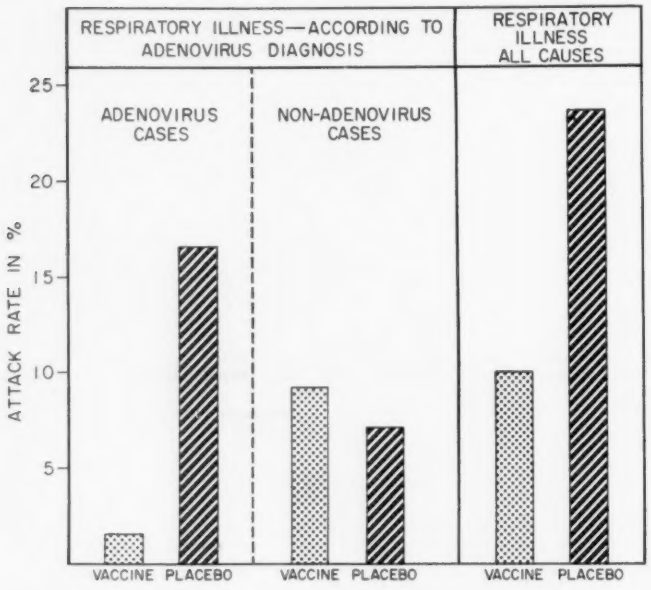

Fig. 2.—Graphic summary of field evaluation of bivalent adenovirus was carried out.

about one week post injection. In the Table, therefore, only those cases which occurred eight or more days post injection are included. During the total period of the study, the attack rates among the 2471 vaccinated and 5767 placebo controls were 11.0% and 23.8%, respectively, giving a protection ratio of 1:2.2, or a 55% reduction in hospital cases of acute respiratory illness, all causes, as a result of vaccination. This sizable reduction in attack rate is markedly increased when the adenovirus cases only in the epidemic are considered. Serodiagnostic CF tests were performed on 59% of the cases in the vaccinated group and on 46% of the controls. Among the vaccinated, 14% and 0.9% of the cases and among the controls 69.7% gave positive tests for adenovirus. Application of these percentages to the over-all attack rates in the two groups yielded calculated adenovirus-specific attack rates of 1.6% and 16.6%, respectively, among the vaccinated and placebo groups. This gave a protection ratio of 1:10.4, or a 90% reduction in cases of adenovirus-caused respiratory illness in the epidemic. The nonadenovirus attack rates were computed from the same data to be 9.3% and 7.2% for the two groups. Possible reasons for the small difference in nonadenovirus attack rates for the two groups are presented in the comment.

A test of the reliability of the vaccine evaluation was carried out by examination, for consistency, of the results by arbitrarily dividing the total study group into three smaller groups, according to time when the vaccine or placebo was administered. It is seen in Table 3 that the results were highly consistent for the three periods. The over-all reduction in attack rates was 50%, 57%, and 57% for the three periods, and these correspond to reduction in adenovirus-specific attack rates of 89%, 90% and 95%, respectively.

The lack of protection from vaccination during the first week post vaccination shown previously [1,3,4] was confirmed in the present study. The attack rate for the vaccinated (24 cases) was 0.97% and for the controls (51 cases) was 0.88% during this period. The vaccine-control ratio of cases was 1.1:1.

Laboratory Findings in the Epidemic.—The great bulk of the adenovirus cases in the epidemic at Fort Leonard Wood was

caused by virus belonging to Type 4. Two hundred fourteen adenovirus strains were recovered from throat washings from 324 cases of respiratory illness in the epidemic. Of these, 201 were Type 4 virus; 8, Type 7 virus; 4, Type 3 virus, and 1, Types 4 and 7 mixed. Types 7 and 3 virus did not appear until late in the epidemic, all strains of these types being recovered after March 11.

There was a close correlation between the virus recovery and serodiagnostic test results. Table 4 shows that 212 of 269 cases (79%) which showed a fourfold or greater rise in CF antibody titer yielded an adenovirus. By contrast, only 2 of 55 (4%) cases negative for adenovirus by CF yielded a virus. These data indicate a close correlation between the serodiagnostic and virus-recovery methods and, hence, the mutual reliability of both procedures as diagnostic tools.

TABLE 4.—*Adenovirus Recovery Results in 324 Respiratory Disease Cases, According to Adenovirus Serodiagnostic Test Result*

Adenovirus CF Test Result	Adenovirus Recovery Result		
	Positive *	Negative	Positive, %
Positive	212 *	57	79
Negative	2	53	4

* 201 strains were Type 4 virus; 8, Type 7 virus; 4, Type 3 virus, and 1, Types 4 and 7 mixed.

A question may be raised concerning the reliability of the CF test for diagnosis of adenovirus infection in persons who were vaccinated recently. The findings shown in Table 5 clearly established the reliability of the test in such persons. Among 17 vaccinated persons who showed a diagnostic increase in CF antibody, 10, or 59%, yielded a virus. By contrast, only 2 of 43 (4%) respiratory cases diagnosed serologically as nonadenovirus yielded an agent. It is important to note, also, that the percentage of isolations from serologically negative cases in the vaccinated group, 4%, was no greater than that for the total group, also 4%, shown in Table 4.

TABLE 5.—*Adenovirus Recovery Results in Sixty-Two Persons Who Developed Respiratory Illness, According to Adenovirus Serodiagnostic Test Result*

Adenovirus CF Test Result	Adenovirus Recovery Result		
	Positive	Negative	Positive, %
Positive	10	7	59
Negative	2	43	4

Tests to determine the etiology of the nonadenovirus respiratory disease cases in the epidemic revealed that influenza was also present. Table 6 shows that 35 (22%) of 196 cases of nonadenovirus respiratory illness gave positive hemagglutination-inhibition tests for influenza. Thirty-four of the cases were Type A, and one was Type B. The actual proportion of cases of influenza in the epidemic was probably greater than shown, since all recruits were vaccinated against influenza shortly after arrival on post and it was impossible, by the diagnostic test employed, to distinguish the titer increase resulting from infection from that due to vaccination. It is worthy of note that among 54 cases diagnosed as adenovirus, none gave a positive test for influenza. This indicated a generally low prevalence of influenza during the study, since a high prevalence, as indicated in previous studies,[9] should have yielded evidence of simultaneous double infections with both adenovirus and influenza in at least a few of the cases.

Comment

The present study, consistent with earlier findings,[1-5] proves beyond all doubt the high degree of efficacy of bivalent Types 4 and 7

TABLE 6.—*Influenza Serodiagnostic Test Results Among Adenovirus and Nonadenovirus Cases of Respiratory Illness*

Adenovirus CF Test Result	Influenza Diagnostic (HI) Test Result		
	Positive	Negative	Positive, %
Positive	0	54	0
Negative	35 *	161	22

* 34 were Type A and 1 Type B.

adenovirus vaccine for preventing acute respiratory illness in newly recruited soldiers and shows, further, the feasibility of commercial production of the vaccine. The 90% reduction in adenovirus-specific attack rates in the present study is consistent with the 98% reduction reported for the previous evaluation at Fort Dix, N. J.[1-5]

In the study at Fort Dix, the vaccine was not given until the men were on post for five to seven days. This delay was obviated in the present study, and the vaccine was given to the recruits within 36 hours of arrival on post. This afforded a special benefit in that the vaccine-protective effect, which becomes evident about seven days post vaccination,[1,3,4] was obtained before the beginning of the explosive outbreak of adenovirus disease, which starts in each company of recruits during the winter at about the second week of training.[14]

During preparation, both the Walter Reed and the Lederle vaccines were passed through relatively porous (medium) sintered glass filters prior to addition of formalin for virus-inactivation purpose. Findings[15] in tests to determine the neutralizing antibody response in man given diluted vaccine have indicated that dilution of the present vaccine more than 1:2 for Type 4 and about 1:27 for Type 7 reduced the mean antibody response and, additionally, diminished the rate of conversion of seronegative persons to the seropositive status. These findings show the limitation of potency of even the present crude-filtered material in inducing maximal benefit in man and emphasize the need to prevent excessive loss of virus during fine filtration now required under the regulations governing adenovirus vaccine production.[10]

The calculation of effectiveness of the vaccine in preventing adenovirus cases, specifically, must necessarily depend on a reliable serodiagnostic test method for separating the adenovirus from nonadenovirus respiratory disease cases in the epidemic. The hot-fixation CF test,[6] as performed, proved a highly reliable tool for this purpose, even in persons who had received adenovirus vaccine. Previous tests[1-5,15] have shown that the CF antibody response to adenovirus vaccine is low or nonexistent and that the postvaccination titer rarely exceeds 1:10. These small antibody responses do not reduce significantly the reliability of the test. This is shown by (*a*) the expected close similarity in attack rates for nonadenovirus cases in the vaccinated and placebo groups and (*b*) the close correlation between the serodiagnostic and virus recovery findings in patients. The slightly higher attack rates for nonadenovirus cases among the vaccinated (9.3%) compared with placebo (7.2%) persons, while of no practical concern, may be explained on two bases: first, in sampling error, and second, in the effect of the vaccine in suppressing adenovirus infection in persons hospitalized for other respiratory illness. Thus, persons hospitalized for nonadenovirus illness but suffering with simultaneous adenovirus infection would be diagnosed, according to the diagnostic criteria, as adenovirus cases. Among most vaccinated persons, the adenovirus infection would be suppressed and the diagnosis would be nonadenovirus. Among nonvaccinated persons, adenovirus infection would not be suppressed and the diagnosis would be adenovirus. These factors would result in a greater apparent nonadenovirus attack rate among the vaccinated than among the placebo controls.

The great need for adenovirus vaccine for preventing acute respiratory illness among new recruits in the Armed Forces is well established,[5,9,14,16-19] and it is contemplated that general use of the vaccine in such persons will be started during the latter part of 1958. The low attack rates, by contrast, among the "seasoned" cadre personnel obviate the need for vaccination in this group.[5,16] Consistent with the pattern in the cadre, adult civilian groups, including families, university students, university employees, and selected cases of acute respiratory illness from hospitals or private

practice, have shown very low attack rates for adenovirus-caused respiratory disease.[5,18] Based on current information, therefore, general use of the vaccine among such persons is not warranted and cannot be justified. There may be a greater need for the vaccine among children and infants. However, the problems of whether the attack rates in children are sufficiently high to warrant general use of vaccine, what particular types of adenovirus should be included in the vaccine, and the evaluation of effectiveness of such vaccine in preventing disease are important challenges for research in the future. In considering use of adenovirus vaccine in any population group, it is important to bear in mind that adenovirus vaccine is not a common cold vaccine and is quite ineffective against this malady.[3]

Summary

Bivalent Types 4 and 7 adenovirus vaccine, prepared by Lederle Laboratories by commercial production procedures, was evaluated in a field study at Fort Leonard Wood, Mo., during the winter of 1957. The attack rate for respiratory illness, all causes, was 11.0% among the 2471 vaccinated persons and 23.8% among 5767 controls who received formalin-saline placebo. The reduction in attack rates for total respiratory disease as a result of vaccination was 55%. The adenovirus-specific attack rates, calculated on the basis of serodiagnostic tests on an approximate 50% sample of cases, were 1.6% and 16.6% for the two groups, and the reduction in cases was 90%. These findings compared favorably with a 98% reduction figure obtained earlier in a study of vaccine prepared in this laboratory and tested at Fort Dix, N. J. The complement-fixation test procedure used proved a highly reliable tool for diagnosis of adenovirus-caused respiratory disease, even among vaccinated persons. The great need for adenovirus vaccine in recruits in the Armed Forces is discussed and contrasted with the apparent lack of need for such vaccine, based on present information, among adult civilians and "seasoned" military groups. Appraisal of need for adenovirus vaccine in children, strain composition of a possible pediatric vaccine, and evaluation of vaccine effectiveness in children are important future research problems.

The Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y., provided the adenovirus vaccine without charge. Col. John Strode (MC), Commanding Officer, U. S. Army Hospital, Fort Leonard Wood, Mo., and his staff cooperated in this study. Technical assistance was given by J. Buford, N. Buterbaugh, D. Darrah, V. Ewing, A. Johnson, D. Levinson, M. Luecking, and R. Schatz. The tissue cultures and tissue culture fluids employed in the study were obtained from Microbiological Associates, Inc., Bethesda, Md.

Walter Reed Army Institute of Research, Walter Reed Army Medical Center (12).

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Xanthomatosis and Coronary Heart Disease

Necropsy Studies of Two Affected Siblings

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The frequent coexistence of familial xanthomatosis and coronary heart disease has been well established.[1-7] There have been, however, relatively few reports of the pathologic findings in such patients,[1,2,5,6,8,9] and in only two reports[1,9] were the histologic findings reported in any detail. To our knowledge, necropsy studies of affected siblings have not been previously reported. The current findings relate to a sister and brother who died in their teens and belonged to a family previously studied by Curtis and co-workers[10,11] and Wilkinson and associates.[12] This family has been recently reexamined[13]; the sister died in the interval between the two studies; the brother, during the course of the present survey. Both parents, although hypercholesteremic, are living and healthy. Four of their other children had died suddenly, presumably of xanthomatous heart disease; of the surviving twelve children, seven have hypercholesteremia without xanthomatosis and are clinically healthy.

Clinical History and Necropsy Findings of Two Patients

CASE 1.—The first patient, the sister, was the 14th of the 18 children and died in 1952, at the age of 16 years. She was a healthy active child, except for skin lesions which were first noted at the age of 2 to 3 years; for some time before death she complained of chest pain on overexertion. She died suddenly while holding her baby niece. On examination in 1947, at the age of 9, numerous tendon xanthomata and tuberous lesions over the buttocks were noted; there was no xanthelasma or corneal arcus. The heart was enlarged; a harsh systolic murmur was heard over the entire precordium, with a thrill in the aortic area and a faint low-pitched diastolic murmur in the mitral area; blood pressure was 118/60 mm. Hg. There were no other abnormal physical findings. Total serum cholesterol was 700 mg. %; phospholipids, 413 mg. %, and total lipids, 1350 mg. %.

Necropsy Findings.—At necropsy, the exterior of the body showed normal development and nutrition for a girl of her age. There were xanthomata over the elbows, wrists, fingers, knees, and Achilles tendon; some of the xanthomata became conglomerate and measured 5 cm. in greatest diameter. On the buttocks, the lesions were polypoid and measured 8 cm. in diameter.

The pericardial sac contained 30 cc. of amber fluid. The heart appeared moderately enlarged and weighed 410 gm. All chambers were dilated, particularly the left ventricle. Marked sclerosis of the coronary arteries was present, but no recent occlusive process was found. The mitral leaflets showed moderate fibrous and atheromatous change, with some shortening of the leaflets and rounding of the margins. However, there was no separation of the commissures or dilatation of the valve, which measured 95 mm. in circumference. The supravalvular portion of the aorta showed only moderate atherosclerosis. A focal region of fibrous thickening of the endocardium beneath the aortic valve cusps on the septal wall formed a pocket-like lesion (Schmenke pocket). Sections through the aortic valve ring revealed marked atherosclerotic thickening and partial calcification. The aortic and pulmonic valves were each 68 mm. in circumference, and the tricuspid valve was 120 mm. The right and left ventricular walls measured 4 and 14 mm., respectively; only a few patchy and small areas of fibrosis were noted on sectioning.

The abdominal aorta showed advanced atherosclerosis which extended into the iliac and renal

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Fig. 1.—Xanthoma tuberosum in Case 2. Many lipid-laden histiocytes are present, and early fibrosis is seen in the central area. Hematoxylin and eosin; reduced about 25% from mag. × 95.

Fig. 2.—Higher magnification of the xanthoma in Figure 1, to show the details of the foam cells. Hematoxylin and eosin; reduced about 25% from mag. × 185.

Fig. 3.—Higher magnification of the above xanthoma, showing many lipid-laden histiocytes around a hair follicle. Hematoxylin and eosin; reduced about 25% from mag. × 266.

Figure 3

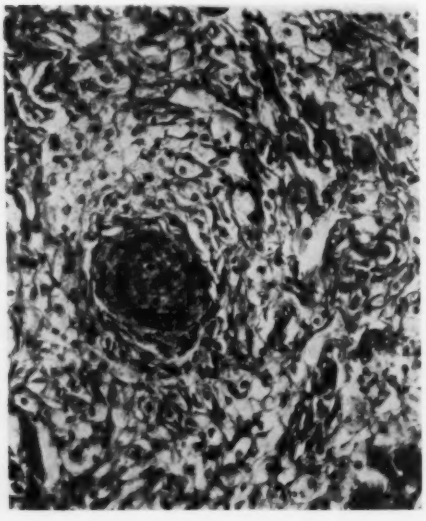

Fig. 4.—Sudan-stained section of the xanthoma from Case 2. The red-brown lipid photographs black and is in abundance in the dermis, with some sparing of the immediate subepidermal zone. The black material on the surface is keratin, which also contains cholesterol; reduced about 25% from mag. × 105.

Figure 4

arteries. Some of the plaques showed softening in the centers. The lungs were moderately edematous. The liver, pale tan in color, weighed 1320 gm. and showed no other abnormalities. The gallbladder revealed slight cholesterosis, but no calculi were present. No other abnormalities were noted on gross examination.

Histologic Examination.—The aorta showed marked atherosclerosis, with many lipid-containing histiocytes around large plaques with central degenerative changes and cholesterol clefts. The base of the aortic valve had atherosclerotic involvement with calcification. Similar changes were noted in the mitral valve. An old atherosclerotic process almost completely occluded a large coronary artery; however, no thrombus was present. There were small patchy areas of myocardial fibrosis with hypertrophic muscle fibers adjacent to these scars.

The lymph nodes were not remarkable. The gallbladder evidenced slight cholesterolosis of the summits of villi. The pancreas and liver were normal. Sections through the xanthomatous lesions on the knee showed an intact epidermis. In the dermis were interlacing bands of connective tissue and many slit-like spaces representing cholesterol clefts. In the margins of the lesions were many pale, mononucleated, vacuolated histiocytes.

Case 2.—The 17th child died in February, 1957, at the age of 13 years. Skin lesions, at first on the heels, were noted at an early age. He was a well-built active boy, but during the last five years of life was restricted by shortness of breath on exertion and occasional chest pain, not always related to exercise. He had fainted a few times. Previous illnesses included chickenpox, German measles, and one attack of tonsillitis, at the age of 8 years. He was well until 24 hours before death, when he developed intense dyspnea and orthopnea, unaccompanied by pain, which failed to respond to sedatives and oxygen therapy, and he died during the night. Physical examination in 1947, at the age of 3½ years, revealed small tendon xanthomata over the heels and dorsum of left wrist. The heart appeared normal in size, but Grade 3 systolic and Grade 2 diastolic murmurs were noted in the aortic area. Total serum cholesterol was 550 mg. %; phospholipids, 357 mg. %, and total serum lipids, 756 mg. %.

Physical examination in January, 1957, revealed extensive tuberous and tendon xanthomata, without xanthelasma but with extensive bilateral corneal arcus. The heart was grossly enlarged, with both systolic and diastolic murmurs at the apex and a rough systolic murmur unaccompanied by a thrill across the base of the heart, A_2 was present; blood pressure was 115/50 mm. Hg. The liver was just felt. Total serum cholesterol was 1033 mg. %. The 12-lead electrocardiogram showed an advanced ventricular strain pattern with regular rhythm.

Necropsy Findings.—The body appeared well developed and nourished, measured 147 cm. in length, and weighed 85 lb. Arterial embalming had been performed prior to necropsy. Numerous raised yellow-brown lesions were present in the gluteal folds; some measured 7 cm. in diameter and were raised approximately 1 cm. above the surrounding skin surface. The gluteal lesions were coalescent and formed a continuous mass extending from the sacral area to the perianal region. Many other xanthomata were noted.

Examination of the head, mouth, and neck disclosed no abnormalities. The lungs were normal in size, with some bilateral basilar congestion. Small yellow raised streaks were present in the intimal surface of the pulmonary arteries.

The heart weighed 400 gm. The pericardium was normal. The left and right ventricles measured 16 mm. and 5 mm. in thickness, respectively. No infarcts or other myocardial lesions were present. All of the valves showed thickening of the cusps, most marked on the aortic and mitral. The chordae tendineae, however, were not thickened or shortened. The circumference of the valves was as follows: tricuspid, 120 mm.; pulmonary, 65 mm.; mitral, 90 mm., and aortic, 40 mm. The proximal portion of the aorta showed marked atherosclerosis, and the coronary ostia were narrowed by deposits of atheromatous material. The coronary arteries were normal in distribution. Focal atherosclerotic lesions markedly diminished the lumina of these

Fig. 5.—Section from Case 2, showing lipid-laden histiocytes beneath the mural endocardium. Myocardium is in the lower portion of the illustration. Hematoxylin and eosin; reduced about 25% from mag. × 105.

Fig. 6. — Section of coronary artery from Case 1, showing atheromatous material beneath the intima; foam cells are fairly abundant at the upper margin of this lesion. Hematoxylin and eosin; reduced 13% from mag. × 125.

vessels. However, complete obstruction was not found in any part of the coronary arterial system.

The spleen measured 15 by 9.5 by 5.5 cm. The gastrointestinal tract showed no abnormalities. The adrenal glands were normal in size and position; the cortices were thin but very yellow. The kidneys were congested; the cortices were 9 mm. in thickness. The liver was normal. No evidence of cholelithiasis or cholesterosis was present in the gallbladder.

The aorta measured 54 mm. in diameter in the ascending part and 32 mm. at its bifurcation. Marked atherosclerotic changes were present in the ascending portion near the arch and in the lower abdominal portion. The ostia of the vessels arising in these areas were narrowed. The renal, iliac, and hepatic arteries showed marked atherosclerosis. No evidence of atherosclerosis was noted in the other abdominal vessels. The remaining gross findings were not remarkable.

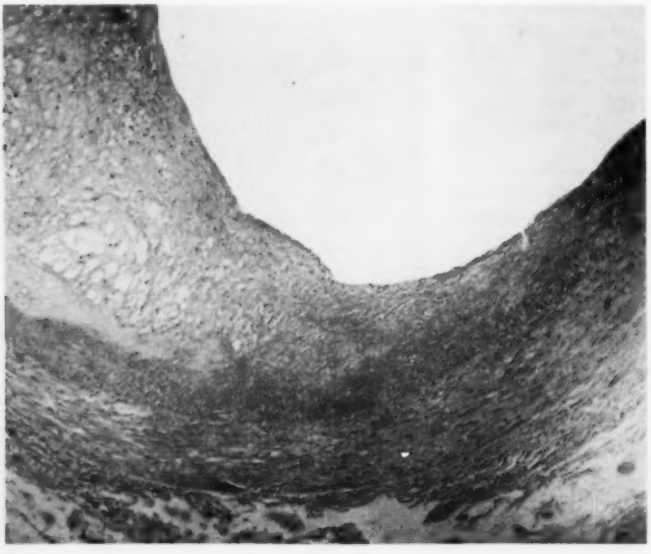

Fig. 7.—Sections of coronary artery from Case 2, showing severe atherosclerosis. Hematoxylin and eosin; reduced 13% from mag. × 130.

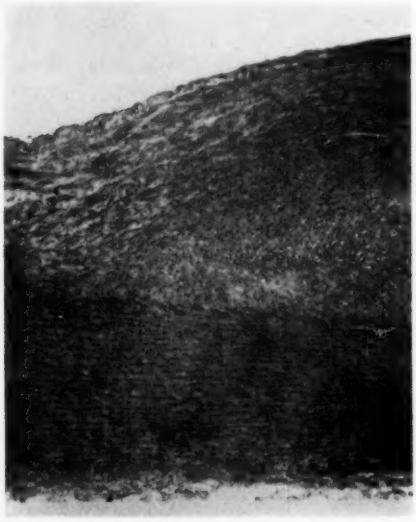

Fig. 8.—Sections of aorta through the margin of an atherosclerotic plaque in Case 2. Hematoxylin and eosin; reduced about 25% from mag. × 130.

Histologic Findings.—Marked aortic atherosclerosis was present. Plaques showed cholesterol clefts, with many foam cells around the margins. A few wandering cells were present in the subepicardial adipose tissue. The myocardium was moderately hypertrophic. No lipid or pigment was present in fat-stained sections. Focal collections of foam cells were seen beneath the mural endocardium, especially just beneath the mitral and aortic valves and, to less extent, on their free margins. Only slight fibrous connective tissue and a few wandering cells were noted around these deposits. The main stems of the coronary arteries showed advanced atherosclerosis in the left artery while the right appeared normal.

The lungs showed moderate congestion, slight edema. Atheromatous deposits were noted in some of the larger vessels. Such plaques were identical in appearance with those in the systemic arteries. Moderate hepatic lipidosis was noted in Sudan-stained sections. No calculi or foam cells were present in the gallbladder. Small collections of foam cells were seen in some of the lymph nodes.

Sections of the skin showed raised plaques covered by intact stratified squamous epithelium which was slightly keratinized. The rete pegs were present and skin appendages were present in the plaques. The plaques consisted of foam cells in large nests and cords with only slight fibrosis. Polariscopic examination of the lipid in the foam cells showed it to be anisotropic (doubly refractile).

Sections of blood vessels were stained with a metachromatic toluidin blue stain, elastic stains (Weigert's and Verhoeff's), and von Kossa's stain. The vessels showed metachromasia which was strikingly diffuse rather than being confined to the typically patchy areas of atheromatous deposits. Only minimal calcium deposits were present in the centers of the lesions and using this method of staining, no calcium was found outside the plaques.

Comment

The alteration in acid mucopolysaccharides, as evidenced by metachromatic staining, is of particular interest. This change, while absent in normal aortas,[14] is commonly found in young persons who have premature atherosclerosis unassociated with hypercholesteremia[15] and in adults with atherosclerosis.[14] The relation between these changes in the staining reaction of the ground substance and the genesis of atherosclerosis remains to be elucidated. The elastic tissue showed degeneration in the immediate areas of and in sites distant from the atherosclerotic involvement. This is in accord with the observations of Taylor[14] that the acid mucopolysaccharide component is derived from degeneration of the elastic tissue.

Only slight differences in the pathologic findings in these siblings were noted. In particular, the calcific aortic stenosis in the sister was possibly severer owing to the fact that the patient was slightly older. It has been reported that calcific aortic stenosis may be hypercholesteremic rather than rheumatic in origin.[5,16]

The presence of foam cells in lymph nodes, mural endocardium, pulmonary arteries, and extravascular xanthomatous deposits illustrates the similarity of this process to the changes seen in hypercholesteremic rabbits. In contrast to the diffuse atherosclerosis seen in cholesterol-fed rabbits, the lesions in human beings with hypercholesteremia show patchy involvement of the arterial system, e. g., in the second patient the left coronary artery showed severe atherosclerosis while the right was normal. Focal factors must therefore have

an important role in determining the site of depositions of cholesterol.

The alteration in the staining properties of acid mucopolysaccharides and elastic tissue is similar to the changes which occurs in "idiopathic" atherosclerosis and possibly those associated with "aging"[14]; such changes are uncommon in normal vessels of this young age group.[15] These findings suggest that the changes in the ground substance are, at least, associated with atherosclerotic processes, though not necessarily a precursor of the change.

Summary and Conclusions

The necropsy findings in two siblings with xanthomatosis who died with coronary arterial disease at the ages of 12 and 16 years, respectively, are presented.

Histochemical studies showed alterations in the ground substance of the arterial walls similar to those seen in patients with atherosclerosis at a later age.

The distribution of foam cells, however, in such tissue as the mural endocardium, lymph nodes, and xanthomas tends to distinguish this disorder from the usual atherosclerotic process and is like the distribution of lipids seen in experimental atherosclerosis of cholesterol-fed rabbits.

Dr. Fred H. Drummond helped in securing permission for necropsy in these cases. The necropsies in the first and second cases were performed by Dr. J. R. Fink and Dr. W. A. DeYoung, respectively. Data regarding the physical examinations of the first patient were taken from the records of Dr. C. F. Wilkinson Jr., Dr. M. T. Fliegelman, and one of us (E. A. H.).

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Case Reports

Muscular Dystrophy in Sarcoidosis

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Sarcoidosis may involve skeletal muscle.[1] Although some reviews [2-4] leave the impression this may be uncommon, other reports [5-7] suggest this is because it is not always looked for. In muscle biopsy specimens from four patients with sarcoidosis, Myers et al.[5] found typical lesions in three, although there was nothing to suggest these had produced any symptoms. Maurice [6] had a patient with muscular dystrophy due to sarcoidosis and then found muscular lesions in 7 of 12 other cases with sarcoidosis. I report a case presenting with a muscular dystrophy.

Report of Case

A dressmaker, aged 39 years, was admitted to the Cardiff Royal Infirmary on Sept. 25, 1954, for muscular weakness and dysphagia. She first noted the weakness in 1944, when for a few weeks her legs felt heavy and she had difficulty in climbing stairs. She recovered completely after eight weeks.

In April, 1954, these symptoms reappeared, and now she also had paraesthesiae, which lasted only about 10 days, but the weakness steadily became worse, and in June the arms and subsequently the muscles of the trunk and neck were also involved. At the end of August she became bed-ridden; at this time a friend noticed that while movement at the shoulders and elbows was very weak, the hands were scarcely affected. A week before admission, swallowing became difficult.

She was a spare pale woman with "myopathic facies" and chronic blepharoconjunctivitis. The skin was normal. She could swallow fluids and solids only slowly, but she did not regurgitate them. She raised her limbs with difficulty and could not raise her head at all. Weakness and wasting of the muscles was generalized and symmetrical. It was most obvious in the muscles of the neck, the shoulder girdle, the upper arm, and the thigh. The affected muscles were atrophic and flabby; they were not tender, and no nodules could be felt. The tendon reflexes were diminished. Plantar responses were flexor, and all forms of sensation, normal. The blood pressure was 110/75. The heart, lungs, abdomen, and fundi were normal.

Investigations.—A muscle biopsy specimen was examined by Dr. Whitely; he found scattered degenerative changes in some of the muscle fibers adjacent to normal muscle fibers; the stroma was infiltrated with fat cells. In a few of the muscle bundles, occasionally near a blood vessel, there were focal lesions composed of a central collection of large pale cells, with an occasional giant cell surrounded by lymphocytes. There was no caseation, and no tubercle bacilli could be found. (Figs. 1 and 2). The following were the results of other investigations: Hb. 95%; WBC 9200; normal differential count (In subsequent counts there was an eosinophilia, varying from 615 out of a total count of 12,300 per cubic millimeter, to 990 out of 5200 per cubic millimeter.); E. S. R. 2 mm. in one hour (Wintrobe); serum protein, albumin 5 gm. %, globulin 4.5 gm. %; electrophoresis, raised γ-globulin value; serum alkaline phosphatase 7.5 K. A. units; serum calcium 11.5 mg. %; lumbar puncture, pressure 120 mm., protein 76 mg. %, cells less than 5 per cubic millimeter; Lange test, normal; W. R. negative; ECG, low voltage in all leads; x-rays, chest, skeleton, and alimentary tract normal; urine, specific gravity 1020, albumin trace, occasional red cells, and a moderate number of granular, hyaline, and cellular casts; 24 hr. excretion of creatinine 195 mg.; creatine 283 mg. (normals, creatinine 600-1500 mg., creatine 0-200 mg.)

Further Course.—She was treated for eight weeks with streptomycin, isoniazid, and cortisone. Her power increased, but despite physical therapy she developed a flexion deformity of 10 degrees at the left elbow, with contractures in the biceps, brachialis, and brachioradialis on that side. After treatment the hilar shadow in the chest x-ray was enlarged. Urinary creatinine excretion was now 328 mg. and creatine, 266 mg. in 24 hours. Three months after discharge from the hospital her muscular power had improved very much, and in July, 1955, she had gained 14 lb. in weight, felt

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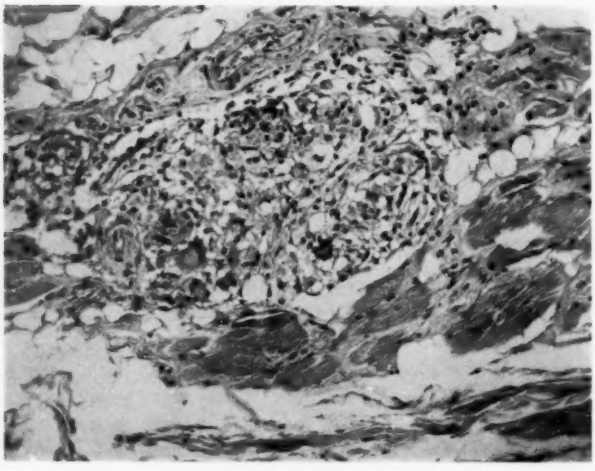

Fig. 1.—Biopsy specimen from left quadriceps; × 130.

well, and could walk unaided. Reflexes were normally brisk. She still had slight dysphagia. The blood pressure was 90/70; the E. S. R., 30 mm. in one hour; the 24-hour excretion of creatine, 400 mg., and the C. S. F. protein, 87 mg. %.

She remained well for two months, but in September, 1955, she became weak again, and a month later she was once more unable to walk. She was readmitted with bronchopneumonia and was now weaker than ever before. The same muscles were affected, and swallowing was more difficult. The blood pressure was 90/70; the Mantoux test, (1/10,000) positive, and she was not given any more cortisone. She was allowed to go home after she had recovered from the bronchopneumonia.

Late in January, 1956, she complained one evening of pain over the heart and died suddenly that night at home. There was no autopsy; it was assumed her death was the result of myocardial involvement."

Comment

The histological appearances were those described by Adams et al.[1] in sarcoidosis; this, with the negative Mantoux test and the raised γ-globulin value, is the basis for the diagnosis of sarcoidosis.

Since Licharew[9] first demonstrated lesions in the muscles in sarcoidosis, alto-

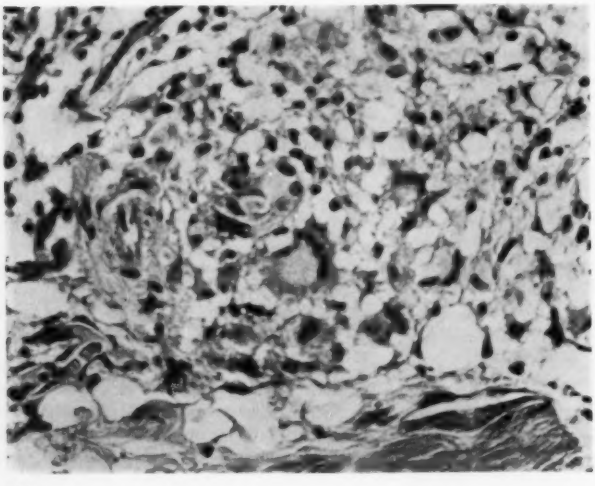

Fig. 2.—Biopsy specimen from left quadriceps; × 310.

Data on Thirteen Patients

Case No.	Author	Sex	Age	Clinical Picture	Examination	Treatment
1	Mucha & Orzechowski (1919) [16]	F	30	Muscular pains; difficulty in walking; muscles partly atrophied, partly hypertrophied	Biopsy	Nonspecific
2	Snorasson (1947) [17]	M	36	Muscular cramps & nodules in arms; progressive fibrous myositis	Biopsy	Nonspecific
3	Bates & Walsh (1948) [8]	M	31	Widespread muscular atrophy	Postmortem	Nonspecific
4	Krabbe (1949) [12]	M	59	Weakness of legs; ataxia; nodules	Biopsy	Nonspecific
5	Powell (1953) [15]	M	18	Progressive weakness of legs; atrophy of muscles	Biopsy	Cortisone; corticotropin
6	de Morsier et al. (1954) [18]	F	61	Weakness of limbs; dysphagia; muscular atrophy	Postmortem	Nonspecific
7	de Morsier et al. (1954) [18]	M	66	Muscular pains & weakness; Korsakow's syndrome	Postmortem	Nonspecific
8	Maurice (1955) [9]	F	72	Muscular weakness & wasting in limbs; nodular fibrous polymyositis	Postmortem	Nonspecific
9	Klotz et al. (1955) [14]	F	30	Pain & heaviness in muscles; firm enlargement of muscles with nodules; contractures	Biopsy	Cortisone
10	Warburg (1955) [19]	F	56	Bilateral symmetrical contractures	Biopsy	Nonspecific
11	Lafon et al. (1955) [20]	M	28	Weakness & wasting of right thigh	Biopsy	Not stated
12	Devic et al. (1955) [10]	F	54	Weakness & wasting of upper arms & lower legs	Biopsy	Streptomycin; isoniazid; corticotropin; cortisone
13	Ammitzboll (1956) [11]	M	38	Fluctuating pain & weakness in shoulders and upper arms; wasting	Biopsy	Corticotropin

gether 53 instances have been described. Of these, 25 had clinical evidence of muscle disease; in the rest the lesions were found incidentally. In 12 of the 25 with symptoms, this amounted to no more than the finding of nodules and there was no weakness. One patient complained of migratory muscle soreness.[8]

Information about the remaining 13 patients with symptoms is given in the Table. In three of these (Cases 4, 6, and 7) the symptoms were in part from concomitant involvement of the nervous system. Ten patients presented with some form of muscular dystrophy. Proximal limb muscles were affected more than distal, except in Devic's[10] case, and although wasting was usual, two patients had an increase in the bulk of muscle. Nodules could be felt in three. Several had fibrous contractures and muscular pains. One had dysphagia. In all but two cases (Cases 11 and 13 in the Table), signs were symmetrical. Only Ammitzboll [11] describes a fluctuating course like that in our patient. The cerebrospinal fluid has been examined before only by Krabbe [12]; in his case it was normal. Sarcoidosis of the nervous system, on the other hand, may produce an increase of cells and protein in the cerebrospinal fluid.[13]

Treatment with cortisone, isoniazid, and streptomycin apparently produced a remission in our patient and that of Devic et al.[10] Others have also had encouraging results with corticotropin (ACTH) or cortisone,[11,14] though Powell [15] noted no effect.

Summary

A patient with sarcoidosis presented with muscular dystrophy. Ten similar cases have been recorded.

Dr. Idris G. Jones gave permission to publish the case and Dr. Paul Fourman helped in preparing this report. Dr. H. J. Whitley did the report on the biopsy, and Mr. J. P. Napper made the photomicrographs.

The Cardiff Royal Infirmary.

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Loculated Interlobar Effusion Associated with Pericarditis

Report of Two Cases

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Several reports of loculated pleural effusion due to congestive heart failure or the "vanishing tumor" of the lung have appeared in the literature. From a review of the literature, Higgins and co-workers [1] considered 41 cases as authentic, and 5 others have since been added.[2,3] One instance of pericardial effusion which disappeared along with the interlobar fluid following diuresis (Kiser,[4] cited by Higgins [1]) and another, of acute and chronic pericarditis with leukemic infiltration of the serosa of the heart,[5] have been noted. Two cases of interlobar effusion associated with pericarditis are reported.

Report of Cases

CASE 1.—A 25-year-old woman was admitted on Feb. 7, 1957, with a history of exertional dyspnea for one year, palpitation for six months, and irregular fever and precordial discomfort for six weeks. Because of a band-like density in the right lung in a roentgenogram she had had antituberculous therapy for the past one month. As acid-fast bacilli could not be demonstrated in the sputum and there was no response to therapy, she was referred by her doctor to the S. M. S. Hospital for investigation of her cardiac condition. On examination, she had rheumatic mitral stenosis, aortic valvular insufficiency, and signs of early congestive failure. A pericardial friction rub, audible over the precordial region, showed presence of acute rheumatic pericarditis. The erythrocyte sedimentation rate was 55 mm. in one hour (Westergren), and an electrocardiogram showed T changes consistent with pericarditis. Roentgenogram of the chest showed slight enlargement of the cardiac shadow with straight left border, congested lung fields, and a band-shaped density in the region of the right transverse fissure. Despite relief of heart failure, the density persisted unchanged. On March 23, the patient had recurrence of pericarditis, with fever and elevation of E. S. R. to 65 mm. in one hour, and a roentgenogram two days later revealed increase in the size of the density and a round lower margin characteristic of an interlobar effusion (Fig. 1). On

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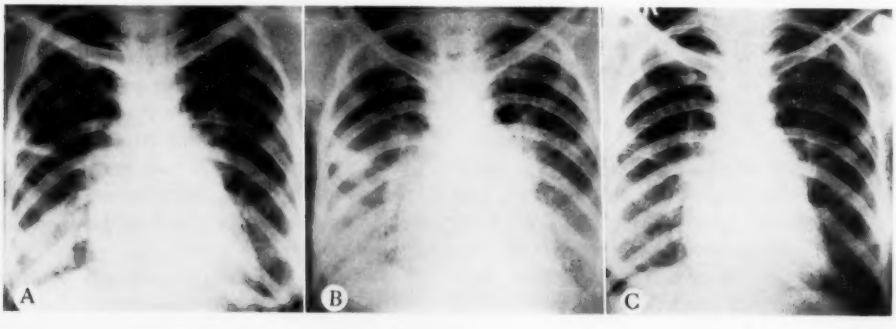
From the Department of Cardiology, Sawai Man Singh Hospital and Medical College; Additional Professor of Medicine.

Fig. 1 (Case 1).—Roentgenograms of the chest. *A*, Feb. 8, showing slight cardiac enlargement, congested lung fields, and a band-like density in the region of the right transverse fissure. *B*, March 25, the density has increased in size, with a round lower margin characteristic of interlobar effusion. *C*, April 2, the effusion has disappeared; only the thin interlobar septum is visible.



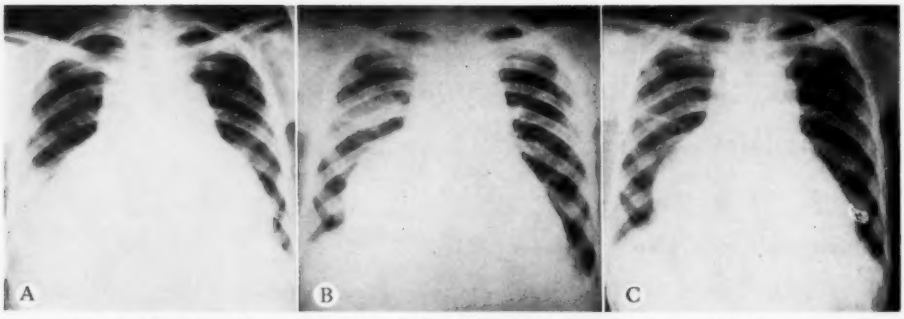


Fig. 2 (Case 2).—Roentgenograms of the chest. *A*, Feb. 6, showing considerable enlargement of the cardiac shadow consistent with pericardial effusion and right-sided hydrothorax with visible interlobar septum. *B*, Feb. 20, interlobar effusion has appeared in the right oblique fissure; there is no fluid in the general pleural space. *C*, Feb. 24, interlobar effusion has disappeared; only the interlobar septum remains visible.

April 2, the density had vanished, leaving a linear shadow of the interlobar septum.

CASE 2.—A 20-year-old man was admitted on Feb. 6, 1957, with acute pericarditis, atrial fibrillation, and congestive heart failure, the illness being of three weeks' duration. The erythrocyte sedimentation rate was 45 mm. in one hour (Westergren), and the arm-to-tongue circulation time was 23 seconds. Roentgenogram of the chest showed considerable enlargement of the cardiac shadow consistent with pericardial effusion and right-sided hydrothorax. At a later date pericardial biopsy[6] and guinea pig inoculation of the pericardial fluid demonstrated tuberculosis as the cause of pericarditis. Hemorrhagic fluid was aspirated from the pericardial and the right pleural cavities. Sinus rhythm was restored on Feb. 10, and heart failure was relieved by Feb. 14, the patient having lost 14 lb. On Feb. 20, however, there was exacerbation of pericarditis, with recurrence of fever and elevation of E. S. R. to 75 mm. in one hour. A roentgenogram showed reaccumulation of fluid in the pericardial sac and an interlobar effusion in the upper part of the right oblique fissure (Fig. 2), though there was no fluid in the general pleural space. The circulation time now was only 11 seconds. The pericardial fluid was aspirated, and four days later the density had vanished. With reaccumulation of the pericardial fluid on March 3, there was no recurrence of the interlobar effusion.

Comment

Increased pressure in the pleural capillaries frequently results in hydrothorax, both in congestive heart failure and in pericarditis. It is, however, of interest that loculated or interlobar effusions have been reported only in congestive failure. In both our cases the interlobar effusion became manifest when the heart failure was well controlled by vigorous therapy with digitalis and mercurial diuretics and its clinical manifestations had apparently disappeared. It has been reported that interlobar effusion may be the only manifestation or subclinical sign of heart failure.[5] The exact mechanism of such an occurrence as well as of interlobar collection of fluid in heart failure is not clearly understood. Such a possibility, appears unlikely in our cases, especially in Case 2 where the arm-to-tongue circulation time had returned to normal and the fluid in the general pleural space had disappeared at the time the interlobar effusion was noted. According to Schwedel,[7] the fluid in the interlobar space disappears rapidly, unlike the fluid in the free pleural space. Again, in both the cases, there was definite evidence of exacerbation of pericarditis, with recurrence of pyrexia and elevation of erythrocyte sedimentation rate, and in Case 2, of increase in the pericardial effusion. It therefore seems most likely that pericarditis was responsible for the interlobar effusion in our cases. It was of interest that the ages of our patients were 25 and 20 years, respectively, while the ages of patients with interlobar effusion due to heart failure reviewed by Higgins and co-workers ranged between 30 and 86 years.

Though a band-like density was seen for nearly two months in Case 1, the densities

characteristic of interlobar effusion in both the cases were transient, disappearing within a period of 10 and 4 days, respectively. It is, therefore, felt that frequent roentgenologic examination may reveal that loculated pleural effusions are not uncommon in patients with pericarditis. It is also suggested that the term "vanishing tumor" of the lung be applied to all loculated pleural transudates resulting from increased pressure in the pleural capillaries, irrespective of its etiology, be it heart failure or pericarditis.

Summary

Two cases of interlobar pleural effusion associated with pericarditis are reported. It is suggested that loculated pleural effusion may not be uncommon in patients with pericarditis.

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, gave permission for the publication of this paper.

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Cryptococcosis

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By 1956 the total number of reported cases of cryptococcosis was over 300,[1-5] and the total has been added to since. It seems reasonable to assume that there may be many other unreported cases, or cases in which Cryptococcus is the likeliest etiology but could not be proved.

The commonest type of infection is of the central nervous system, but cases have been reported of primary cryptococcosis in the skin [2] and one case of visceral cryptococcosis that presented a clinical picture of granulocytic leukemia [3] before death. There are four reports of Cryptococcus infection of the eye, all made postmortem.[4-8] Cryptococcosis has also been found to be responsible for cases of adrenal insufficiency, coexistent with Hodgkin's disease, tuberculosis, and histoplasmosis, in which cases the clinical findings were of a rather bizarre nature. The clinically confused picture often found has led to the declaration that "perhaps it can be postulated that any central nervous system complication in a prolonged chronic illness should immediately raise the question of fungus superinfection, especially Cryptococcosis." [9] We have one such case of proven cryptococcosis to give added weight to this statement.

Submitted for publication Nov. 14, 1957.

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Report of Case

A 60-year-old retired grocery-store manager was first referred to us by an internist, with a complaint of headache and vertigo of approximately six month's duration, in January, 1956. The ocular examination was essentially normal, with normal acuity and intraocular tension and no evidence of intraocular inflammation.

The patient was again seen in late May, 1956, complaining of haziness of vision in the left eye but normal acuity, with stringy vitreous opacities not previously noted and a whitish area in the upper temporal periphery of the left eye. The patient was still under treatment by the internist without any real positive physical findings, and the left eye showed little change in the ensuing two months. His vision remained normal. A few vitreous opacities and an area in the upper temporal periphery which was somewhat yellowish but ill-defined still remained.

The patient was seen on Oct. 15, 1956, for the third time, and he stated that the vision in the left eye had been very bad for the previous four or five weeks, coincident with the eye becoming inflamed and painful. At this examination, there was marked congestion of the left eye. Large yellowish mutton-fat K. P. were visible. The pupil was small and secluded. Intraocular tension was 56 mm. The right eye was essentially normal.

The patient was hospitalized, and measures were taken to control the inflammation and the tension. The iris was resistant to all attempts at dilatation, and, although there was some lessening of congestion with hydrocortisone (Hydrocortone) and the use of acetazolamide (Diamox), the tension remained approximately 45 mm. On Oct. 26, 1956, an iridectomy was attempted.

At surgery, the iris was found to be markedly thickened, and attempts to free it from the lens were unsuccessful, as it appeared to be adherent along its entire posterior contact with the lens.

During the patient's hospitalization, the internist had again carried out a thorough examination, without finding any explanation of the etiology or explanation for his seeming debility, increased

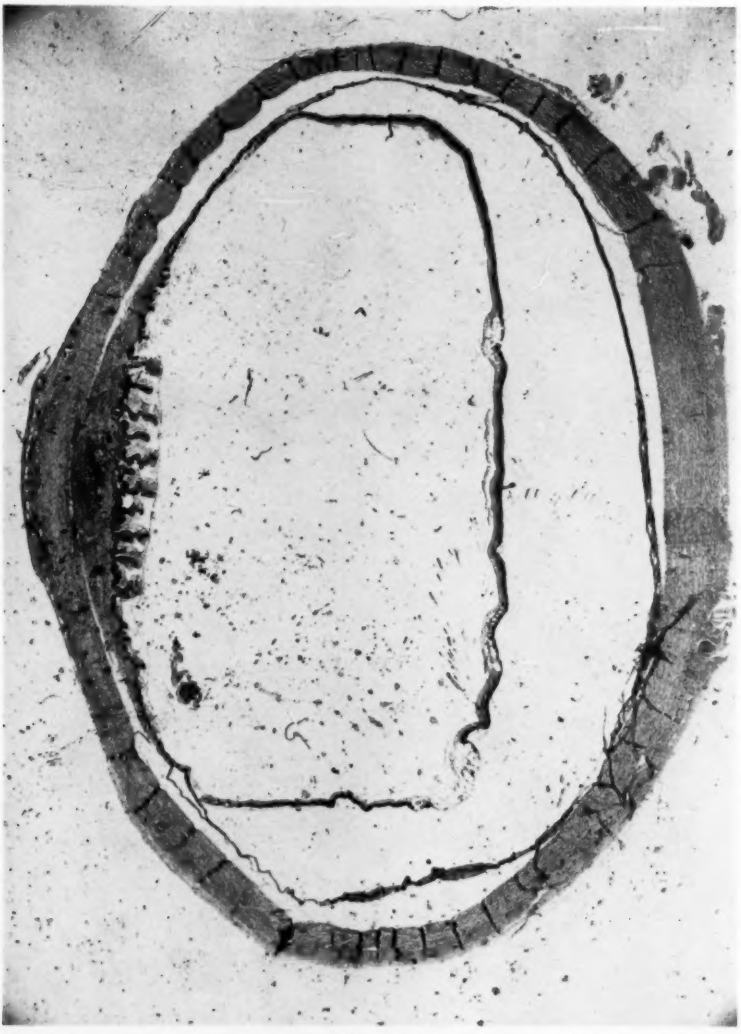

Fig. 1.—Low-power view of eye, showing uveitis and panophthalmitis, with synechiae between lens and iris. Grossly the eye was sectioned in half, with the lens remaining in place. The anterior chamber was shallow, and there is evidence of atrophy of the iris with posterior synechia. There was a little irregularity and piling up of the surface of the retina in the posterior pole and also some choroidal atrophy seen in the equatorial region. The section shows that it has been cut rather eccentrically, with only a small portion of the cornea and anterior chamber showing. The cornea appears to be edematous, with some swelling of the epithelium. The corneal fibers are widely separated by fluid. From specimen prepared by Dr. Miles Foster and Dr. H. G. Gifford, Pathology Department, Clarkson Hospital, Omaha. Description of pathology submitted by Dr. H. G. Gifford, Pathologist. HDE stain; × 16.

headache, and occasional periods of disorientation, other than his age.

On Nov. 2 the family agreed to enucleation, which was uneventful, and the patient was dismissed home before the pathologic report on the eye was returned. The initial pathology report was acute and chronic endophthalmitis with Candida infestation of retina and choroid.

A later detailed pathology report (Figs. 1 and 2) described a lytic process present throughout the

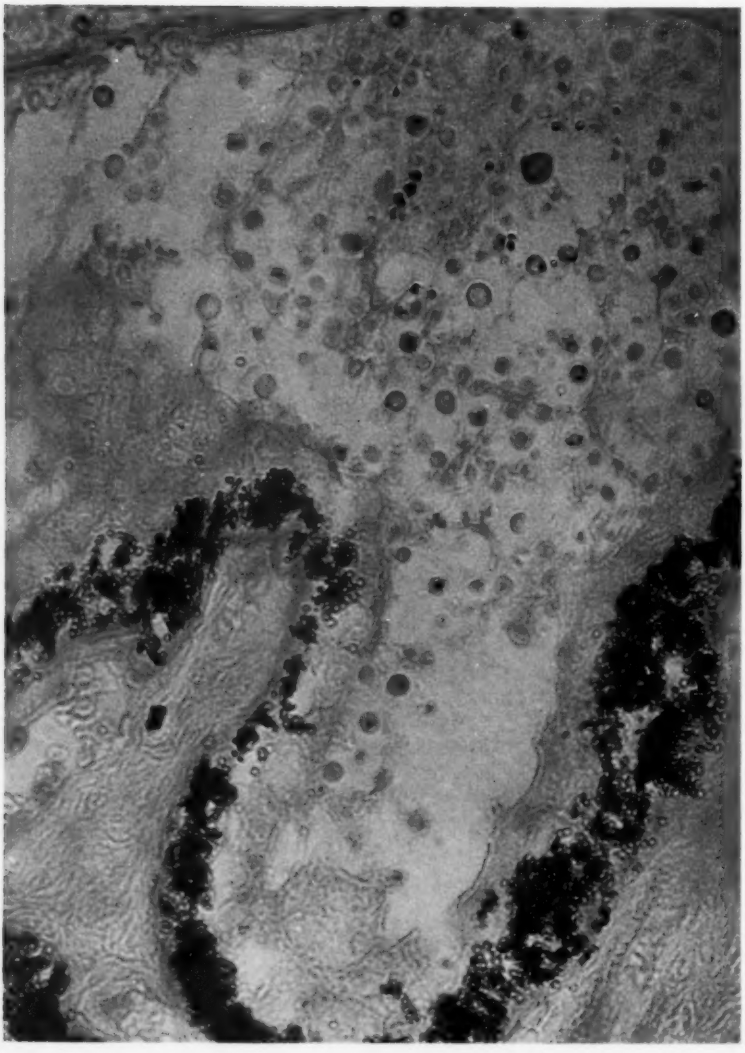

Fig. 2.—Cryptococcus neoformans in retina (periodic acid-Schiff stain). Yeast-like bodies have invaded the detached retina and have caused a lysis of the retinal cells, giving the appearance of an explosive force. There is very little evidence of inflammation surrounding the destroyed retinal tissue. The choroid shows a moderate amount of round-cell infiltration. Yeast-like bodies were best seen on the surface of the choroid, where they appear to be destroying the pigment epithelium. The chamber angle is infiltrated and is being destroyed. This is a lytic process without inflammatory reaction. These yeast-like bodies when stained with Hotchkiss-McManus stain show clearly as purple-staining spheres; the size is variable, and occasionally they are budding into single buds. There were no mycelia present in these sections. Some of the larger bodies appear to be elliptical, like small sharp-pointed footballs with a second line in the capsule on one side. These larger bodies are also surrounded by a clear zone in the surrounding tissue. Special stains with mucicarmine indicated a mucopolysaccharide in the capsule and would probably classify this yeast-like fungus as Cyptococcus, which may also be confused with Candida. Prepared from specimen submitted by Dr. Miles Foster, Pathologist, Clarkson Hospital, Omaha. Description of pathology submitted by Dr. H. G. Gifford, Pathologist. Periodic acid-Schiff; ×400.

eye without inflammatory reaction. Yeast-like bodies were found in the iris, on the choroid, and invading the detached retina.

Hotchkiss-McManus and mucicarmine stains delineated the yeast-like fungus and indicated a mucopolysaccharide in the capsule. A diagnosis of cryptococcosis would appear to be definite.

Pathologic Diagnosis. — Cryptococcus; uveitis with secondary glaucoma (clinical).

Although the right eye remained essentially normal and the left socket was well healed, the patient continued to be more disoriented at home and still disturbed. He was transferred to the Veterans' Hospital on Nov. 27, 1956. On admission to the Omaha V. A. Hospital, there was a history of periods of dizziness and mental confusion associated with episodes of weakness of arms and legs. The patient had been gradually deteriorating mentally and physically for the past several years; this was secondary to what his physicians thought was cerebral arteriosclerosis. He had also complained of rather consistent back pain, which was thought to be due to arthritis.

He had hit his head in a fall 11 months prior to admission and had received a head injury in an auto accident 22 years before.

He was received on the medical service for treatment of what was thought to be cerebral arteriosclerosis, osteoarthritis, and possible central nervous system fungal infection. The remaining history and system review were not contributory.

Physical Examination.—Pertinent findings revealed a poorly nourished, asthenic, white man, who was rather confused and depressed, with marked dulling of his sensorium and a definite loss of relationship to his present surroundings. There was a marked facial weakness, with a droop of the right side of the face. The abdomen showed definite signs of weight loss, and the liver and spleen were both palpable at the costal margin but did not descend on deep inspiration. The prostate was moderately enlarged to about Grade II and was firm. The left eye was surgically enucleated, and the socket contained serous drainage. Right eye EOM, pupillary reflexes, conjunctiva, and sclera were normal. Funduscopic examination revealed Grade II arteriosclerotic changes.

Neurological examination demonstrated moderately hyperactive tendon reflexes on the right and relatively normal reflexes on the left. There was a questionable Babinski reflex on the right, with possible Chaddock sign present. A positive Romberg sign was present. Brudzinski and Kernig signs were absent. There was some weakness of the right side, most pronounced in the right arm and including (in the hand) the interossei and some of the extensor and adductor muscles of the forearm and upper arm. There was no neck rigidity and no loss of skin sensation, vibratory sense, or positional sense noted. The remainder of the physical examination was noncontributory.

Laboratory and X-Ray Findings.—Hematology: Hemoglobin 10.3 gm.; hematocrit 38%; sedimentation rate 20 mm. in one hour; WBC 7550; neutrophils 75%, lymphocytes 20%, monocytes 1%, eosinophils 4%. A trace of sugar was found in the urine and 3 to 5 WBC per high-power field. Prothrombin time at admission was 16 seconds for the patient, with a control of 13 seconds. The prothrombin time was maintained at therapeutic levels of 25 to 35 seconds with bishydroxycoumarin (Dicumarol). Spinal fluid examination revealed 10 cells per cubic millimeter, with polymorphonuclear leukocytes 4 and lymphocytes 5; sugar 12.5 mg. per 100 cc.; chlorides 658 mg. per 100 cc. No micro-organisms were seen in Gram- or acid-fast-stained smears of spinal fluid. Routine, acid-fast, and fungus cultures were negative. Blood urea nitrogen was 11.5 mg. per 100 cc. Blood total protein was 6.9 gm. per 100 cc.; albumin, 4.6 gm.; globulin, 2.3 gm. Van den Bergh test, direct, was 0.35 mg. per 100 cc.; indirect was 0.45 mg. Alkaline phosphatase was 1.5 units. Cephalin flocculation was negative in 24 and 48 hours. Thymol turbidity showed 0.5 units.

Chest x-ray was within normal limits. X-ray of lumbar, cervical, and thoracic spine revealed rather far-advanced osteoarthritis, marked lipping and bridging, and some associated osteoporosis. X-rays of the skull, posteroanterior, anteroposterior, and lateral, showed no pineal shift or space-occupying lesion. EEG demonstrated α-rhythm of 7 to 9 cps, with a good deal of θ-activity and a few δ-bursts. There was slightly greater amplitude of δ-waves on the right side (Fig. 3). Sleep record was negative. Interpretation was abnormal diffuse slow record. ECG was within normal limits.

Hospital Course.—On admission, the patient was given absolute bedrest with commode and a low-sodium diet. Temperature was within normal limits. Pulse was 90 or more during his hospital stay. Blood pressure on admission was 140/90 and leveled off at an average 128/80. Neuropsychiatric and neurology consultation on Dec. 3, 1956, showed the patient to have diffuse cerebral and general arteriosclerosis, with minor foci of encephalomalacia. Deep reflexes were absent on the right lower extremity but present on the left. He had an ataxia, and the Babinski sign was positive bilaterally. The recommendation of the consultant was to continue the anticoagulant therapy. He was transfused to bring his blood cell count up to normal, and he was maintained with bishydroxycoumarin. Pentylenetetrazol (Metrazol) and nicotinic acid were administered in an attempt to improve his mental status. With this treatment he gradually improved clinically. On Dec. 2, 1956, he was given cynocobalamin (vitamin B_{12}), 1000 mg.

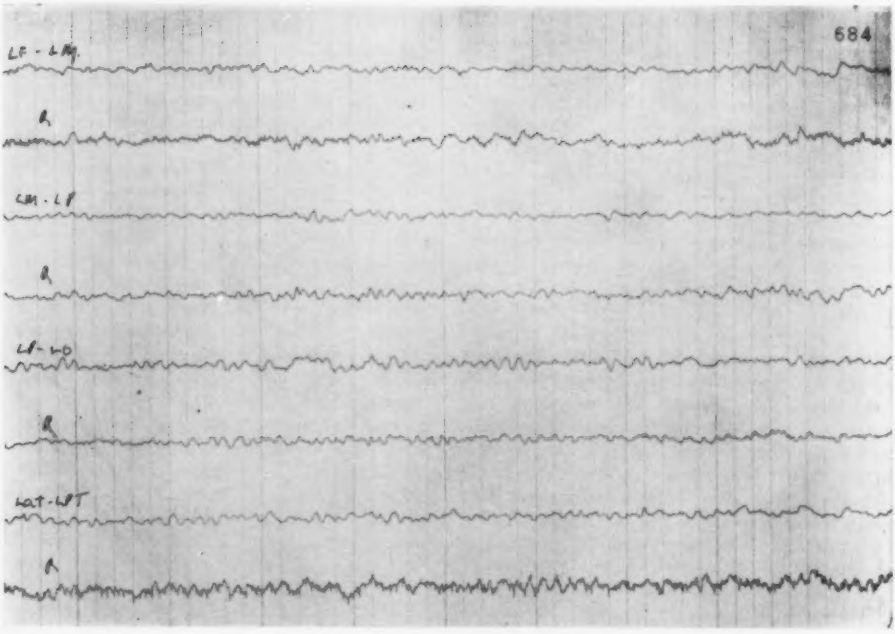

Fig. 3.—Electroencephalographic record revealing abnormal diffuse slow waves.

daily, with vitamin B-complex daily intramuscularly on the recommendation of the neurologist. On Dec. 4, 1956, a spinal tap was done, and the spinal pressure was 90 mm. of water. The fluid was mildly xanthochromic but otherwise not remarkable, which tended to confirm the diagnosis of cerebrovascular accident with gradual resolution. The patient continued to improve gradually, with little difficulty in ambulation. At 7 p. m. on Dec. 9, 1956, he went to the bathroom and shortly thereafter was heard to fall by a nurse standing outside the door. The patient was found sitting on the floor, with a contusion over the right parieto-occipital region. He was noted to have a general diaphoresis and a mild general pallor. The right eye was open; the pupil responded and was not dilated. Blood pressure was 148/80, pulse, 96. He was retching and trying to vomit. Neurological consultation revealed the deep reflexes to be intact and abdominal reflexes, absent. Bilateral Babinski sign was present, but the patient could move his extremities. A spinal tap revealed a pressure of

Fig. 4.—Cut section of adrenals, showing the firm white caseous-like necrosis replacing most of the medulla.

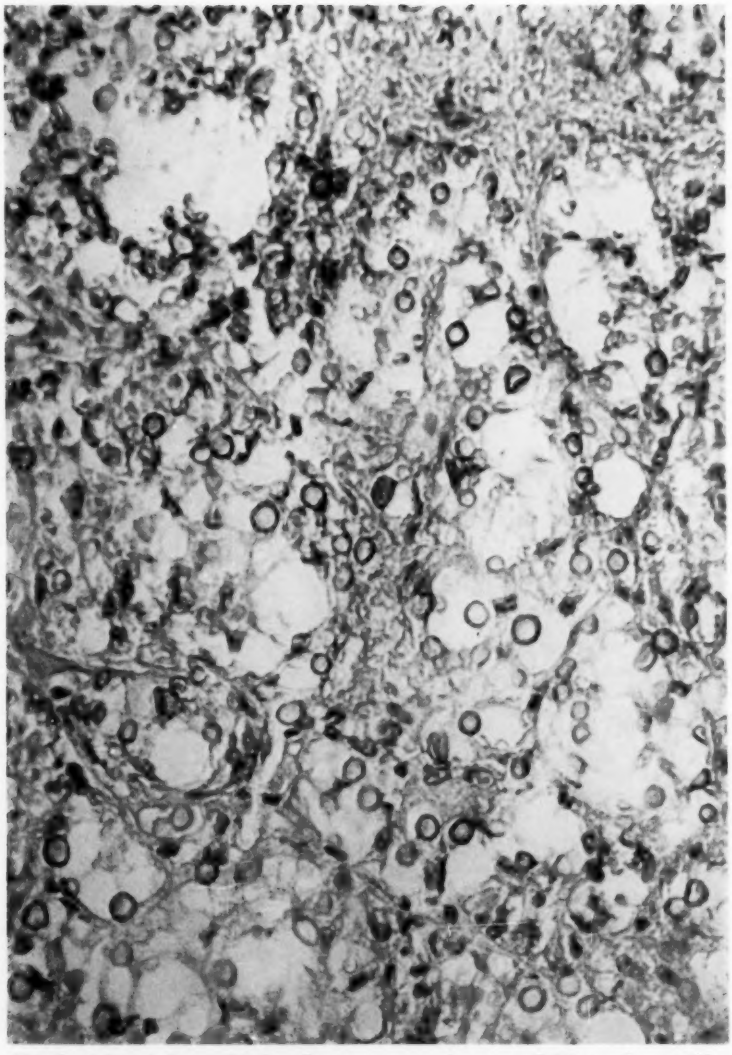

Fig. 5.—Adrenal tissue, showing Cryptococcus neoformans. Gridley stain; × 400.

600 mm. of water, with fluid at first clear and then bloody. Neurological impression was (1) intracranial hemorrhage after fall, (2) possible skull fracture, and (3) cerebrovascular accident previous to fall. The patient's course was steadily downhill, with increased loss of vital signs, elevation of blood pressure to 210/120, and fall of pulse rate. He died in coma at 6:20 a. m. on Dec. 10, 1956.

Gross Autopsy Findings.—Pertinent gross findings included the following.

1. Adrenal Glands: The adrenals were about four times normal size and on cut section revealed a firm white caseous-like necrosis involving the medulla (Fig. 4). Only a thin rim of cortex remained. A portion was taken for culture.

2. Head: Scalp. There were some ecchymoses over the left parietal region and what appeared to be a hematoma 8 cm. in diameter. There was marked fresh hemorrhage into the scalp in this area and also into the left temporal muscle.

Calvarium. There was a 14 cm. linear fracture that extended from the occipital region down to and through the petrous portion of the temporal bone along the ridge of the left middle fossa.

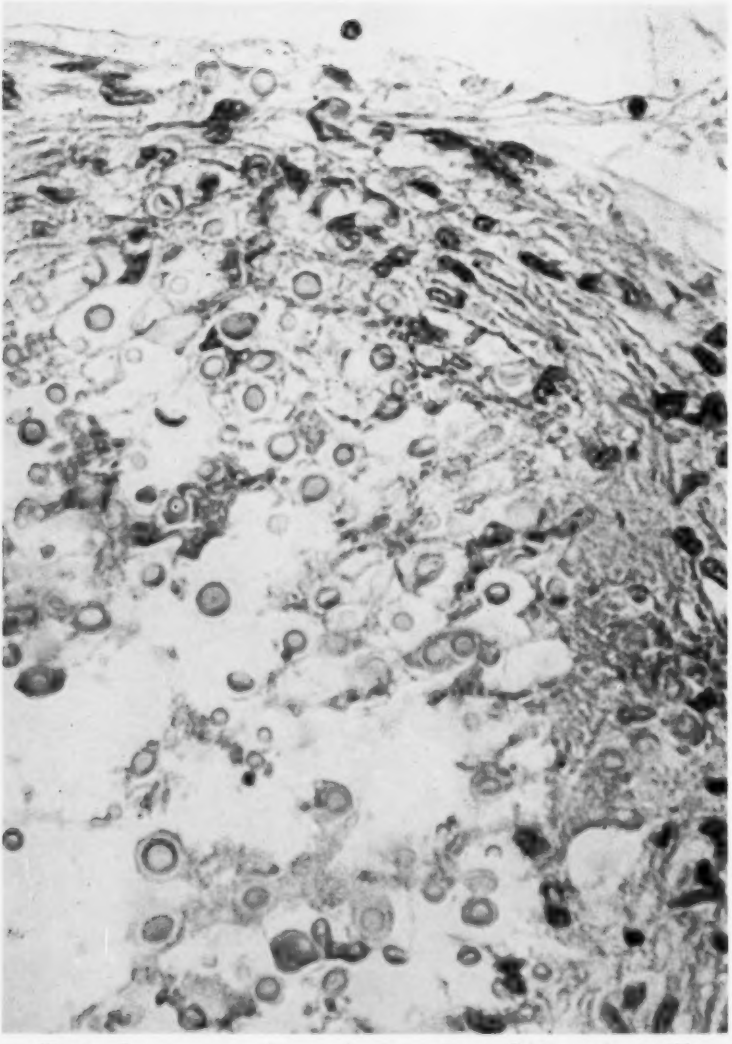

Fig. 6.—Cryptococcus neoformans in the meninges. Gridley stain; × 400.

Dura and Dural Sinuses. Between the dura and brain there was about 75 gm. of clotted and unclotted blood. The brain appeared slightly depressed in this region.

Brain. The brain weighed 1300 gm. There was an 8.5 cm. area of subarachnoid hemorrhage in the left temporal parietal region and some beneath the olfactory lobes. On cut section there was hemorrhage into the cerebellar tissue and into the pons. The hemorrhage appeared fresh and was scattered over an area 5 cm. in diameter. The basilar arteries were thickened and somewhat calcified. The coronary arteries showed a Grade II atherosclerosis.

Microscopic Autopsy Findings.—Pertinent microscopic findings included the following.

1. Adrenal Glands: The medulla was replaced by necrotic material, with a small amount of calcium scattered throughout. There were numerous yeast cells, 5μ to 10μ in diameter, scattered through the necrotic material and in the adjacent tissue (Fig. 5). A fair margin of normal-appearing cortex was present. The yeast cells were positive to the mucicarmine stain.

2. Liver: Moderate passive congestion and marked vacuolation of the nuclei was seen.

3. Pancreas: Mild fatty infiltration. Most of the islands of Langerhans were hyalinized.

4. Cerebellum: Intracerebellar hemorrhage with necrosis, numerous corpora amylacea with mild thickening, and fibrosis of the leptomeninges with scattered foreign body giant cells. Within the thickened meningeal structures were numerous yeast cells (Fig. 6) similar to those seen in the adrenal glands and also positive to the mucicarmine stain.

5. Pons: Intrapontine hemorrhage. Necrosis, perivascular hemorrhage, and thrombosis were present in some of the smaller vessels. There was a granulomatous meningitis present about the vessels in this area, with scattered yeast cells, positive to the mucicarmine stain.

6. Cerebral Cortex: Subarachnoid hemorrhage with granulomatous meningitis and scattered yeast cells positive to the mucicarmine stain were present.

Pathologist's Conclusions.—The immediate cause of death was subdural, subarachnoid, pontine, and cerebellar hemorrhage. The subdural and subarachnoid hemorrhages were secondary to his fractured skull. The pontine and cerebellar hemorrhages were most likely due to spontaneous bleeding, aggravated by bishydroxycoumarin therapy, although there is the possibility that they may have been traumatic. The intrapontine and cerebellar hemorrhage most likely precipitated the fall that produced the fracture of the left parietotemporal bone.

The cryptococcal meningitis was responsible for the somewhat bizarre clinical symptoms and periods of memory deficit. The possibility cannot be excluded that this meningitis may have precipitated the fall producing the hemorrhages.

The changes seen in the pancreas and liver are those seen in diabetes.

Microbiological Studies.—The spinal fluids drawn on Dec. 4 and on Dec. 10, 1956, were negative on Gram- and acid-fast-stained smears and culturally negative for common pathogenic bacteria, mycobacteria, and fungi.

Brain and adrenal tissue were homogenized, and direct microscopic examination of the homogenate revealed thick-walled budding yeast cells 5μ to 15μ in diameter. India-ink preparations of the homogenate demonstrated capsules 3μ to 5μ thick surrounding the organisms. Acid-fast smears were negative, as were cultures for mycobacteria and the common pathogenic micro-organisms. Fungus cultures of the homogenate became positive in 5 to 10 days. The growth was cream- to tan-colored, moist, slimy, and mucoid, and India-ink preparations revealed encapsulated yeast cells. Mice given inoculations of the homogenate became sick and died at an average time of four or five weeks after. Autopsy of the mice revealed gross lesions on the omentum and peritoneum. Microscopically the lesions were granulomatous, with necrotic material containing budding encapsulated yeast cells positive to the mucicarmine stain. In the experience of the Armed Forces Institute of Pathology, Cryptococcus is the only one of the commoner fungi, with the exception of an occasional Blastomyces, which takes the mucicarmine stain.[10] Cryptococcus may be differentiated from other yeast-like fungi by a mucicarmine-positive capsule containing demonstrable acid mucopolysaccharide.[23] * Cultures from mouse tissue were positive for the same fungus as the brain and adrenals.

The organism was identified as Cryptococcus neoformans.

Comment

This case presented a number of problems of diagnosis and treatment.

Most probably the patient had a long standing Cryptococcus meningitic infection, which accounted for the mental deterioration of the previous six months. This may have been preceded by minor arteriosclerotic changes in the cerebral arterioles, but these were not prominent at postmortem examination. An extension may have occurred from the meninges along the optic tract and optic nerve sheath into the posterior chamber of the eye. From this point, the fungus passed by way of the lymphatic system and other channels to infect the uveal tract, with eventual development of a secondary glaucoma. An iridectomy was attempted, and later an enucleation of the eye was done.

The insidious course of this disease was aided by an occult diabetes, manifest by pathological findings of hyalinization of islands of Langerhans and vacuolation of nuclei of the liver. There had been no essential clinical findings of diabetes, although one urine specimen showed a trace of sugar and another, 1+ acetone.

C. neoformans grows well in a medium rich in sugar, and this may account for its dissemination to other parts of the body—

* Mayer's mucicarmine stain. M. F. Gridley, Manual of Special Staining Techniques, Armed Forces Institute of Pathology, 1957, pp. 188-189. Complete technique is outlined in Littman and Zimmerman,[6] p. 160.

in this case to the adrenal glands. Here the organism apparently grew with abandon, producing by its presence in the adrenal gland a granulomatous reaction which crowded the normal tissue to one side of the gland. Sufficient functioning adrenal cortex was left to provide adequate stores of corticoids for electrolyte and blood pressure maintenance, as demonstrated by normal blood pressure and normal serum electrolytes, especially sodium and potassium. The lack of more overt diabetic findings may have been a reflection of decreased glucocorticoids, although we have no direct evidence on this score.

Because of a misconstruction of the etiology of the mental changes and neurological pattern, this patient was treated with bishydroxycoumarin, which promoted a bleeding tendency leading to his death. This suggests that all organs removed at surgery should be routinely cultured for fungi and injected into mice to determine pathogenicity. A procedure of this type would tend to increase the case finding of Cryptococcus, pathogenic Candida, Histoplasma, Blastomyces, and Coccidioides and also permit a more adequate diagnostic evaluation and therapeutic program.

Summary

A case of glaucoma, secondary to Cryptococcus uveitis and Cryptococcus meningitis (Torula) is presented wherein the diagnosis was confused owing to bizarre mental changes and neurological findings. The relationship of occult diabetes mellitus to the dissemination of the organism with adrenal granulomatous involvement is discussed. The need for case finding through use of mucicarmine stain technique and culture on Sabouraud's or other fungal media and mouse inoculation is stressed, in order to diagnose and treat more adequately an increasing incidence of infection.

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Treatment of Tietze Disease with Prednisolone

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Although Tietze [1] reported the syndrome of painful enlargement of the costal cartilages in 1921, this condition received little attention in American literature until recently. Tietze's original description of 5 cases has been followed by reports of more than 160 other examples of the same disease. The first American paper on Tietze's syndrome was written in 1953, and subsequently there have been at least five additional major papers produced in this country.

Tietze disease has been variously referred to as the costochondral syndrome, painful swelling of the chondrocostal region, costal chondritis, stress fracture of upper ribs, and prominent costal cartilages. Since the pathogenesis of the disease is unknown, the eponym designation is useful at the present. Tietze originally suggested that tuberculosis or wartime malnutrition might have been etiologic factors. Subsequent authors have proposed that buckling of the cartilage due to an inflammatory reaction in the ligaments immediately behind it,[2] trauma to the rib or interarticular sternocostal ligament induced by heavy physical work or coughing, or rheumatic disease of this ligament may be responsible for the syndrome. No consistent histologic picture has become apparent on study of the affected costal cartilages. Pathologists generally report such findings as hyperplasia of the cartilage and thickening of perichondrium, muscle, fascia and adjacent ligaments, and apparently histologically normal cartilagenous tissue.

Clinically, Tietze's syndrome is characterized by painful enlargement of one or more costal cartilages and adjacent ribs associated with local tenderness. The second rib cartilage alone is reported to be involved in about 60% of the cases,[3] and the left side is more commonly affected than the right. The condition is also known to occur at a sternoclavicular junction. Generally, swelling and pain reach a maximum within a day or two and then gradually subside over a period of three to four weeks.[4] However, some residual enlargement may remain for months or even permanently. Characteristically, the skin overlying the tumor mass is normal in appearance and there is no local warmth or erythema. Pain in the affected area may precede the onset of tumorfaction. Although this pain is increased by deep inspiration, coughing, and sneezing, it is dull in character in contrast to the sharp stabbing pain of pleurisy. The intensity of pain and tenderness varies considerably. In some cases no therapy other than reassurance is required, whereas in others the pain may be severe and the tenderness, exquisite.

Various forms of treatment have been employed. Local application of heat and the use of acetylsalicylic acid may provide symptomatic relief. Deep x-ray therapy, mechlorethamine hydrochloride (nitrogen mustard), local infiltration with procaine, corrective postural exercises, the use of bedboards, and surgical removal of the involved cartilage [5] have been advocated. Since all reports of the costochondral syndrome indicate that it is an entirely benign and self-limited condition, it is particularly desirable that therapeutic measures be moderate in nature. However, when pain is severe and persistent, the customary conservative measures often meet with indifferent results. Although total excision of the offending tissue produces a reliable and permanent cure, this vigorous management of a rather innocent disease

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seems inappropriate. We recently had occasion to cope with this problem of painful swelling of a costal cartilage and came upon what appears to be a simple and effective remedy.

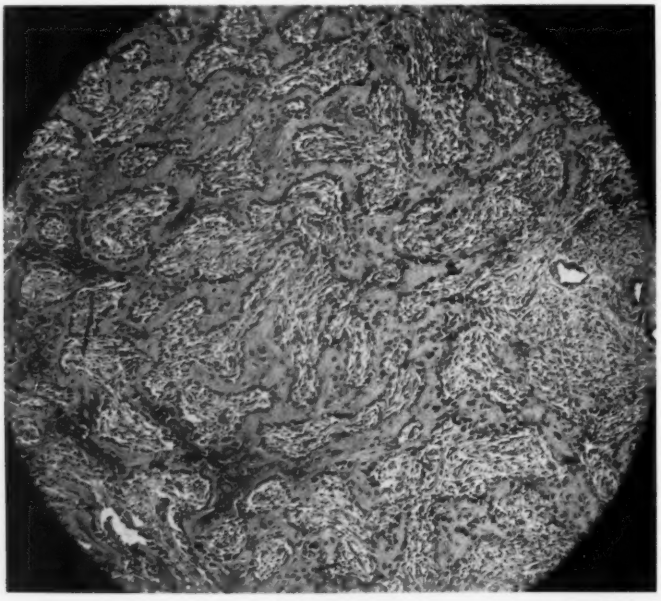
Report of Case

A 35-year-old Caucasian man came to the clinic on June 7, 1957, complaining of chest pain of five-to-six days' duration. The pain was gradual in onset and was situated in the left lower anterior chest wall. Its character was dull, and its intensity, moderate. Pain was increased by deep inspiration, coughing, sneezing, twisting or turning movements of the torso, bending forward, and external pressure in the area of the seventh costal cartilage. A chest x-ray taken on the day of examination was not remarkable. The patient's lower ribs were immobilized with an adhesive tape strap, and this produced immediate diminution of pain. Two days later, the patient noted increasing pain and tenderness associated with local swelling in the affected area. He was admitted to Mercy Hospital, Janesville, Wis., on June 10, 1957, because of severe chest pain. Physical examination revealed blood pressure 130/84, pulse 88, and temperature 99.2 F orally. There was a tender fixed fusiform mass, roughly 4 cm. in length, which appeared to represent a localized expansion of the seventh costal cartilage in the left anterior axillary line. This mass was plainly visible on inspection and was elevated 1-2 cm. The overlying skin was normal in appearance and mobile. Complete physical examination was otherwise not remarkable. The chest x-ray and spot film of the tumor mass showed no abnormality. The complete blood cell count revealed hemoglobin 15.1 gm.; leukocytes 9800, with 65% neutrophils, 5% eosinophils, 22% lymphocytes, and 8% monocytes, and sedimentation rate 5 mm. in one hour. The test for C-reactive protein was negative, and the urinalysis showed no abnormality.

The patient was treated with acetylsalicylic acid, meprobamate, hot packs, and a chest binder. These measures, however, afforded him inadequate relief of pain. His distress was considerable, although he had been assured that the condition was harmless and self-limited.

Surgical biopsy on June 14, 1957, confirmed that the tumor mass represented cartilagenous enlargement at the costochondral junction. Sections were sent to The Mayo Clinic, and these were described as follows: "In our opinion your slides numbered 1155-57 show the active new bone formation such as one gets following a fracture or perhaps some strange inflammatory process. We see no evidence of malignancy, so please let me know if it metastasizes" (Figure). Culture of bone curettings from the costochondral junction produced a nonhemolytic streptococcus.

On June 16, 1957, all existing therapeutic measures were canceled, and treatment with prednisolone, 5.0 mg. every six hours orally, was initiated. Lessening of pain began within 24 hours. In an additional 24 hours the patient was entirely pain-free, and there was minimal or no tenderness at the tumor site. He was dismissed



from the hospital on June 20, 1957, feeling quite well. Prednisolone (Meticortelone) therapy was discontinued abruptly after an additional eight symptom-free days. In 24 to 36 hours pain had recurred with almost its original intensity. It persisted in this degree for another day, and by July 1, 1957, the pain was somewhat diminished. Reexamination of the patient on July 3, 1957, showed definite recurrence of tenderness in the tumor mass. The patient was again given prednisolone, 2.5 mg. three times daily, and over a period of 24 to 36 hours pain and tenderness once again subsided. Prednisolone was again discontinued on July 16, 1957, and the patient has subsequently been symptom-free. Diminution in the size of the costal cartilage was first noted by the examiner on July 6, 1957. The mass was gone on July 24, 1957, but there was slight residual enlargement of the rib cartilage. This was again noted on follow-up examination four months later.

Comment

The rather remarkable influence of prednisolone upon the course of the above case of Tietze disease prompted us to review the literature for reports of similar experiences by other clinicians. In 1955 Celio and Nigst [6] reported treating two cases of Tietze disease with local injections of hydrocortisone. Case 1 was given three injections within a period of one week. After 12 days the swelling was entirely gone and pain had diminished. Another injection was given at that time, and after an additional 10 days there was no spontaneous pain and only slight discomfort on pressure. In Case 2 the swelling disappeared in a matter of a few days after the injection, and the patient was free of discomfort 10 days after the local injection of hydrocortisone. The patients were followed up for one year, with no apparent recurrence, and the authors recommended local hydrocortisone as a very effective procedure.

Summary and Conclusions

A case of Tietze's syndrome and results of treatment with prednisolone (Meticortelone) are described. An earlier report of successful steriod therapy (hydrocortisone injected in loco) is noted. Further trial of prednisolone in the treatment of this uncommon disease is warranted. The drug manifested a favorable influence upon the clinical course of the case which is reported.

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Addendum

Subsequent to submitting this paper we have employed prednisolone therapy in another case of Tietze disease. A 22-year-old Caucasian man came to the clinic on Dec. 19, 1957, because of severe pain of two days' duration emanating from the right sixth costochondral junction. He had been in good health until a week and a half earlier, when he developed acute coryza and bronchitis. During the act of coughing, chest pain was exquisite. Only slight prominence of the affected area was noted on inspection, but palpation revealed enlargement and marked tenderness of the costochondral junction. Again, x-ray and laboratory data were not remarkable, and on Dec. 20, 1957, treatment with prednisolone, 7.5 mg. every six hours orally, was instituted. In approximately 24 hours spontaneous pain was markedly diminished, and in an additional day it had abated entirely. Although there was some residual local tenderness, this was minimal and was of little concern to our patient. After gradual and uneventful reduction in the prednisolone dose, steroid therapy was terminated on Jan. 10, 1958. It is concluded that prednisolone produced a favorable effect upon this patient's disease, comparable to that noted in the earlier case.

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Periodic Neutropenia

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Periodic or cyclic neutropenia is considered to be a rare hematological disorder, characterized by a chronic rhythmic recurrence of severe neutropenia or agranulocytosis at approximately three-week intervals. Ordinarily the worst phase of the neutropenia extends for five to eight days, and this may be associated with a compensatory rise in the monocytes or eosinophils, particularly if there is a normal number of leukocytes present.[1] During this same period serial bone marrow studies have been reported by some observers to show a complete suppression of the granulocytic series, from the myeloblast to the mature neutrophil [1-5]; others have noted only a maturation arrest at the promyelocyte level, a result probably due to the lack of serial aspirations.[6-9] During the normal or relatively normal intervals between the episodes of severe neutropenia, the bone marrow is normal. On two occasions there have been abnormal concentrations of platelets associated with this disease; one author [10] reported a thrombopenia, and another [11,12] described platelets which "became exceedingly numerous." The sedimentation rate ordinarily is normal or near normal, but Borne [13] and Chaiken [1] reported elevated sedimentation rates during the episodes.

During the periods of severe neutropenia minor infections frequently occur, typical of which are furunculosis, oral ulcers, cystitis, and upper respiratory infections. In contrast to other forms of agranulocytosis, serious infections are unusual in these patients. Only six cases [1,5,8,13-15] have included a severe infection as one of the clinical features, and these infections all included a pneumonia as part of the situation. Two [8,15] of the six patients who had pneumonia died during the infection. Ischiorectal infections have been noted in three cases.[2,6,13] During the intervals between the times of severe neutropenia, these patients have been free from infections. During two pregnancies there was a similar freedom from infection in one of the patients.[16] In Barling's patient [17] the symptoms were worse during pregnancy.

This disease has occurred at all ages, from infancy to the eighth decade of life; however, in almost half of the patients it had its start in infancy. It has been reported starting in four patients [2,5,6,18] over the age of 40, the oldest [5] of whom was 76 (who was 79 years old in 1951). Once the disorder is present, it persists without interruption. This has been the rule for all the patients except for one,[11,12] who had episodes lasting several months in 1919, 1926, and 1936 but was free from the disorder the rest of the time. This disease has been present for as long as 34 years (from infancy to the time of death) before the patient [15] finally died of pneumonia.

The etiology of this disorder is unknown. Dr. Reimann [19] has included this entity in the broader designation of periodic disease, which includes periodic fever, periodic abdominalgia, intermittent arthralgia, angioneurotic edema, anaphylactoid purpura, and periodic paralysis. He believes that these disorders are somehow related because they have in common regular short episodes of disease recurring over many years, without affecting the general health. Thompson [15] tried to establish a relationship with the menstrual cycle and reported a case of a male who had diabetes insipidis associated

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with an elevation of the urinary gonadotropins and decrease in the urinary estrogens just prior to the onset of severe neutropenia, such as occurs in a female just before menses. Other investigators [2,4,7,20,21] found no correlation with the menstrual cycle and found no fluctuation of hormones related to the neutropenic episodes. Natelson [9] pointed to the possibility that the occurrence of lymphomas in two patients was more than just coincidental and stated that cyclic neutropenia might be a rare manifestation of lymphomas and that, as such, both might be related to a disturbance of reticuloendothelial origin. A congenital origin was expounded by Coventry [16] because of the fact that almost half the cases began in infancy. A familial tendency is possible, as Vahlquist [3] noted a leukopenia in the father of his patient. Chaiken [1] felt that an allergic etiology was remote, as only one patient [4] had such a symptom, that being asthma.

Coventry [16] states that for a diagnosis of this disorder a patient should have a history of recurrent infection over a period of years, have recurrent cycles of neutropenia during the infections, and have good health in spite of the infection and neutropenia.

Therapy to alter the cyclic changes of the neutrophils generally has been unsuccessful, the exceptions being during administration of corticotropin (ACTH) and after splenectomy. Monto [5] described a marked improvement of the neutropenia and well-being of the patient 72 hours after the use of corticotropin. Commenting on this patient, Chaiken [1] and Natelson [9] stated that one could not be certain that the improvement was due to a specific effect of corticotropin but rather due to the combination of the antipyretic and the antitoxic effect of corticotropin coincident with the expected cyclic remission of the neutropenia. To substantiate this opinion, Reimann,[4] Chaiken,[1] and Natelson [9] noted no amelioration of the severe neutropenia during the use of corticotropin; in fact, Natelson and Reimann noted a more marked lowering of the total white blood cell count. Chaiken noted symptomatic improvement while the patient was receiving corticotropin.

Coventry [16] made the enlightening comment that splenectomy will be beneficial in this disease only if the spleen is considerably enlarged, a situation which is very infrequent in young patients but present in all of the patients who had the onset of the disorder after the age of 40. Thirteen patients have now been subjected to splenectomy for cyclic neutropenia. Six of these patients received permanent benefit, and these patients all had spleens which were two to four times larger than normal; only one of these patients was under the age of 24 at the onset of the disease. The other seven patients who had no beneficial effect had normal-sized spleens and were under 24 years of age. These results completely substantiate Coventry's astute observation concerning this form of therapy.

Report of Case

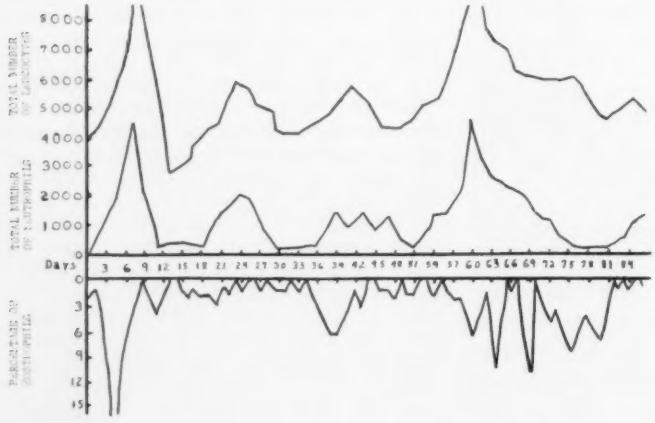
This 28-year-old Negro gravid woman was seen approximately two weeks prior to admission of Dec. 25, 1955, for fever and sore throat, the latter having been present for one week. Examination of the throat at that time revealed enlarged tonsils covered with an exudate. Enlarged tender submandibular lymph nodes were also present. For this the patient received procaine penicillin, 600,000 units, but she did not return for further penicillin therapy. Three days prior to admission the patient returned to the emergency room, this time having a cough, rhinorrhea, and temperature of 100.8 F. Examination at this time revealed the presence of an infected pharynx and an occasional moist rale at the base of the right lung. The patient was thought to have a possible early pneumonia and was given procaine and crystalline penicillin, 600,000 units of each, a cough mixture containing diphenhydramine (Benadryl), acetylsalicylic acid, and phenylephrine (Neo-Synephrine) nose drops. The patient did not return for subsequent therapy. Three days later the patient was again seen in the emergency room and was noted to have painful labored respirations and a productive cough containing white frothy sputum. She was afebrile and had a normal pulse rate. Examination of the lungs revealed moist rales and ronchi throughout. The x-ray of the chest was normal. A blood cell count was done at this time, and this showed a complete absence of neutrophils; because of this finding the patient was admitted to the hospital.

The past history was as follows: The patient had had asthma for seven years but had had no recent episodes. Four years previously she had pneumonia without sequelae. Two years previously she was treated for syphilis. She had repeated episodes of pelvic inflammatory disease, which were treated with penicillin. Seven months prior to admission she developed a pyoderma, which cleared without therapy. She had been drinking excessively for 11 years. The family history revealed that her mother had asthma and a "touch of TB." Physical examination at the time of admission revealed the additional finding of a prolonged expiratory phase to her respirations.

The laboratory findings were as follows: The hemoglobin was 10.5 gm. per 100 cc. The white blood cell count was 5800 per cubic millimeter, of which there were no neutrophils, 1% stabs, 48% lymphocytes, 46% monocytes, 2% eosinophils, 3% plasmocytes. The routine urinalysis was within normal limits. The Bence Jones protein was not present. The bleeding time was 2 minutes; the clotting time, 4 minutes 20 seconds. The prothrombin time was 83%. There were 268,000 platelets. The heterophil value was within normal limits. The cold agglutination test was negative. Smears for L. E. cells were normal. The sternal bone marrow aspiration revealed a cellular specimen containing many promyelocytes and myelocytes, a normal number of metamyelocytes, a few stab cells, but only a rare neutrophil. The other cells in the bone marrow were normal. The bone marrow was considered to be diagnostic of maturation arrest of the granulocytic series. The N. P. N. was 16 mg. %; serum protein, 5.2 gm. %; serum albumin, 2.7 gm. %, and the serum globulin, 2.5 gm. %. Sputum test for acid-fast bacillus was normal. The VDRL test was positive, and the Kolmer test was 3+.

The patient was thought to have an acute asthmatic bronchitis and an agranulocytosis, possibly due to a drug sensitivity. The next day the white blood cell counts of the previous five years (four in number) were reviewed. This revealed that the patient had had a white blood cell count of 4500, with 14% neutrophils, 5% stab cells, 71% lymphocytes, 9% monocytes, and 1% eosinophils, five years previously, in September, 1950, with only one of the four white blood cell counts being normal and the two others showing a neutropenia. This suggested the possibility of a periodic cyclic neutropenia, and daily white blood cell counts were obtained during a three-month period of hospitalization (Figure). The Figure shows a general periodicity in the number of neutrophils present. The greatest depression of the neutrophils occurred at variable intervals, ranging from 16 to 29 days between each of the most marked periods of neutropenia. An eosinophilia was present periodically throughout the three months of observation, but correlation with the neutropenia was not too apparent. There appeared to be a greater eosinophilia at those times when the degree of neutropenia was least in evidence, but this was not strictly so. The eosinophilia was as much as 17% of the total white blood cell count. Two subsequent bone marrow aspirations were performed when the peripheral white blood cell count was near normal, and these specimens were found to be completely normal.

Hospital Course.—The patient was treated symptomatically for her respiratory distress and given penicillin for a six-day period. X-rays of the chest taken three days after admission revealed minimal infiltration in the right lower and middle lung fields which was consistent with minimal interstitial pneumonitis. Also three days after admission the patient became asymptomatic and re-



Serial blood cell counts of three months, showing the periodicity of the neutropenia and its relationship with the eosinophilia.

mained so throughout the rest of her hospital course. Approximately two months after her admission to the hospital, at the time of her expected date of termination of pregnancy, the patient was delivered of a stillborn child. Except for the fetal death, the pregnancy was not otherwise complicated. The patient received penicillin prophylactically for nine days after the delivery.

The patient was discharged from the hospital on March 22, 1956, and did not return to keep her appointments. On May 9, 1956, the patient was again admitted to the hospital. She stated that she had frequent sore throats and colds since discharged from the hospital and had had a continuous cold for the two weeks prior to this time. Four days prior to admission she developed chest pain, fever, chills, cough, blood-streaked sputum, and shortness of breath. Examination at that time revealed fever (temperature of 105 F), pulse of 136, and respirations of 48 per minute. There were moist rales over the lower third of the right posterior chest, associated with a pleural friction rub. The rest of the examination was unrevealing. The white blood cell count was 3350, with 2% neutrophils, 89% lymphocytes, and 9% monocytes. The serology was positive for syphilis. X-ray of the chest showed a segmental pneumonitis involving the right middle lobe and the left upper lobe. The patient was given penicillin and streptomycin and became afebrile in 24 hours. The patient recovered quite rapidly and was discharged after seven days of antibiotic therapy. While she was in the hospital the cyclic nature of the neutropenia and the presence of the eosinophilia were again in evidence.

After discharge on May 16, 1956, the patient was seen periodically in the outpatient department. On June 24, 1956, she was treated for an asthmatic attack. On July 30, 1956, she was given therapy for a bacterial pharyngitis. She developed a cystitis in September, 1956, at which time her white blood cell count was 3650, with 5% neutrophils, 70% lymphocytes, 21% monocytes, 2% eosinophils, and 2% basophils. She recovered from this illness without difficulty. Two months later, on Nov. 4, 1956, the patient was admitted to the hospital because of an incomplete abortion, from which she recovered without complication. Her blood cell counts at this time were normal. Two and one-half weeks later, she again had cystitis, and this was treated on an outpatient basis. On Feb. 4, 1957, she was noted to have developed a perirectal abscess, which was treated with incision and drainage only. On Feb. 21, 1957, the patient was treated for a pharyngitis. From that time to September, 1957, the patient was asymptomatic. In September, 1957, she again returned to the emergency room because of a sore throat, but, since she was without fever and the examination of the pharynx was normal, she was dismissed without therapy. A white blood cell count again revealed marked neutropenia.

Comment

Since 1946 there has been made reference to a total of 24 cases [1-6,8,9,13,14,16,18,21-24] of cyclic neutropenia. Prior to that time, only 6 other cases [4] had been recorded, which together makes a total of 30 cases. It would seem that this disorder is truly not so rare as originally contemplated and, thus, substantiates Reimann's [4] original opinion as mentioned when he had collected a total of 16 cases.

This patient fits the criteria necessary for a diagnosis of this disorder as outlined by Coventry,[16] as she has a history of recurrent infections or asthmatic attacks for a period of nine years; she has had recurrent cycles of neutropenia, frequently associated with infections, with the neutropenia known to be in existence for seven years, and, finally, she appears to be in good health in spite of the affliction and is free of infection in the intervals between the neutropenia.

By way of distinction I believe this is the first person of her race (Negro) to have this disease; however, a thorough search was not done to make certain of this fact. Of the two patients [4,16] who were reported to be pregnant, one was free of her symptoms while pregnant, possibly indicating a hormonal basis for this disease. Our patient, however, like Barling's patient, had frequent upper respiratory infections while pregnant, thus somewhat refuting this relationship.

As was noted of many of the cases, there was a compensatory rise in the number of mononuclear cells at the time of severe neutropenia, but, instead of an associated increase in the number of eosinophils at that time, as was reported by others, there was a marked decrease in the eosinophilia, which, during the intervals between neutropenia, reached as high as 17%, one of the highest reported in this disorder. In two other cases the eosinophilia was higher, being 20% in one [6] and 25% in another.[24] This patient

had a normal platelet count, as did all but two of the other patients. While only three bone marrow aspirations were performed, two during the normal interval, the one done during the severe neutropenia showed an arrest of the granulocytic series but not at the myeloblastic stage, as was noted in other case reports.[1-5] The bone marrow was aspirated the day prior to a rise in the neutrophils in the peripheral blood, and this fact may account for the presence of more mature granulocytes in the bone marrow at that time. The other two bone marrow specimens taken during the intervals between severe neutropenia were normal, which finding correlates with other observers.

At 10 weeks post partum this patient developed a pneumonia, a finding present in a total of six patients.[1,5,8,13-16] Later she had an ischiorectal abscess, a complication which has occurred in three of the cases.[2,6,13] Only one other patient [4] has had asthma associated with this disease, a frequency too small to be significant in relation to an etiological factor. So far she still fits Coventry's [16] criteria for nonoperability; that is, she had the onset of the disease as a young adult and has had no enlargement of the spleen, as yet.

Summary

A review of 30 cases of periodic neutropenia collected from the literature is presented to emphasize that this disease is no longer extremely rare. The indication for splenectomy is outlined, and the cases having had splenectomy are reviewed to substantiate that this indication is correct.

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Raynaud's Syndrome Associated with Idiopathic Cryoglobulinemia and Cold Agglutinins

Report of a Case and Discussion of Classification of Cryoglobulinemia

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It was only a decade ago that the name "cryoglobulinemia" was proposed by Lerner and Watson,[1] in a case of purpura appearing upon exposure to cold and associated with a cold-precipitable globulin in the blood. Such a protein was accidentally discovered in 1933 by Wintrobe and Buell[2] in a patient with multiple myeloma, who exhibited purpura, Raynaud's phenomena, and retinal vein thrombosis. Although very small traces of cryoglobulins have been demonstrated in a variety of pathological states, only a limited number of patients with large amounts of cryoglobulins have thus far been reported. Essential, or idiopathic, cryoglobulinemia is a rare condition, only nine cases having been previously reported.[3-11]

The association of cold agglutinins with symptoms of peripheral vascular disorders has been observed on a number of occasions.[12-15] High cold agglutinin titers have been described most commonly in primary atypical pneumonia,[16] but they also are found in trypanosomiasis,[17] tropical eosinophilia,[18] and occasionally in mumps orchitis[19] and infectious mononucleosis.[20] High titers have frequently been associated with acute hemolytic episodes and are believed to be responsible for some of these cases of hemolysis.[21]

The association of essential cryoglobulinemia and cold agglutinins in high titer has been reported only once previously.[7] This patient did not exhibit evidence of cold sensitivity but had an acute hemolytic anemia. Cold agglutinins have occurred in a case of cryoglobulinemia secondary to chronic lymphatic leukemia[22] and also in a case of cryoglobulinemia associated with multiple myeloma.[23]

The purposes of this paper are to report and discuss a case of essential cryoglobulinemia associated with a high titer of cold agglutinins in a patient who exhibited acrocyanosis and Raynaud's phenomena and to suggest a classification of cryoglobulinemia.

Report of Case

An 85-year-old white man was first seen by one of us (C. G. G.) after admission to the Danville Memorial Hospital on Nov. 8, 1956, because of Raynaud's phenomena involving the fingers and toes, of five days' duration. He came under the care of his attending physician* first on Feb. 25, 1956, at which time he was found to have a mild respiratory infection infection with dyspnea of two weeks' duration. He gave a history of ankle edema and mild orthopnea. He also complained of left-sided headache of approximately two to three weeks' duration. Physical examination at this time revealed blindness in the right eye; the ears, nose, and throat were negative; there was complete edentia. The heart sounds were of poor quality; no murmurs were heard. By physical examination the heart appeared to be enlarged, and the blood pressure was 230/120. The lung fields were clear by auscultation and percussion. The peripheral pulses were present, and there was no ankle edema. The patient was digitalized and maintained on 0.1 mg. of digitoxin daily, along with reserpine, 0.25 mg. twice daily. He was given a multiple vitamin preparation.

On March 3, 1956, he was seen and reported improvement. He complained only of constipation and nervousness. At this time the blood pressure

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* This case is presented through the courtesy of Dr. Henry Wiseman III, Danville, Va.

Fig. 1.—Digits of right hand. Note the subungual petechiae and the dark, dusky color of the right fifth finger, which was more cyanotic than the other three fingers.

Fig. 2.—Digits of left hand. Cyanosis of the digits was present, along with the subungual petechiae, and an ecchymosis is observed in the nail bed of the index finger. All nail beds were cyanotic.

was 210/90, and his medications were continued. He was advised to use a mild laxative. On March 12, 1956, he was seen again; his nervousness continued. His blood pressure was 220/80, and his reserpine was reduced to 0.25 mg. daily.

On March 20, 1956, the patient complained of having had an episode of faintiness. His blood pressure was 200/90. He continued to complain of nervousness but otherwise was doing well.

On April 20, 1956, he was seen complaining of a mild cold. Oral temperature was 100 F. Examination of the nose, throat, heart, and lungs was negative. Blood pressure was 150/90.

On May 5, 1956, he was seen because of enuresis and nervousness. The blood pressure was 180/90. Urological consultation was advised.

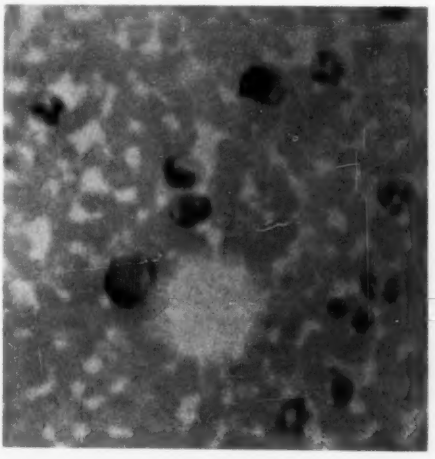
He was not seen again until August 8, 1956, when he was seen because of mild respiratory infection, and was given 400,000 units of penicillin.

On Nov. 3, 1956, the patient was brought to his physician's office by his daughter, who reported that he had been rather inactive for the past several weeks but had not complained. She had noted marked discoloration of the fingers and toes on occasions. Examination of the extremities revealed marked cypnosis of the digits of both hands. The second, third, and fourth toes of the right foot were similarly involved. The changes were thought to represent early gangrene, but, since the patient was asymptomatic, he was advised to resume his reserpine, 0.25 mg. twice daily, and was placed on priscoline, 25 mg. three times daily. When he was seen again, on Nov. 8, there was reported improvement in the appearance of his hand; however, there was marked cyanosis noted in the second toe of the right foot and the first, third, and fourth fingers of the right hand. The left hand was relatively free of involvement except for cyanosis of the left fifth finger. The patient had begun to complain of pain in the extremities and was admitted to the hospital at this time.

Further questioning after admission to the hospital revealed that upon exposure to cold there was blanching of the digits followed by more marked cyanosis.

Physical examination revealed a well-preserved man for the age of 85. The left pupil was deformed by surgery and did not respond to light. The right pupil reacted to light, but the lens was opaque. The fundus of neither eye could be visualized. The neck was supple. There was no adenopathy. The chest was clear to auscultation and percussion. Examination of the heart revealed

Fig. 3.—High power photomicrograph of bone marrow smear showing a background of red cells with a few young white cells, two normoblasts and five segmented neutrophils. No abnormal cells are seen.



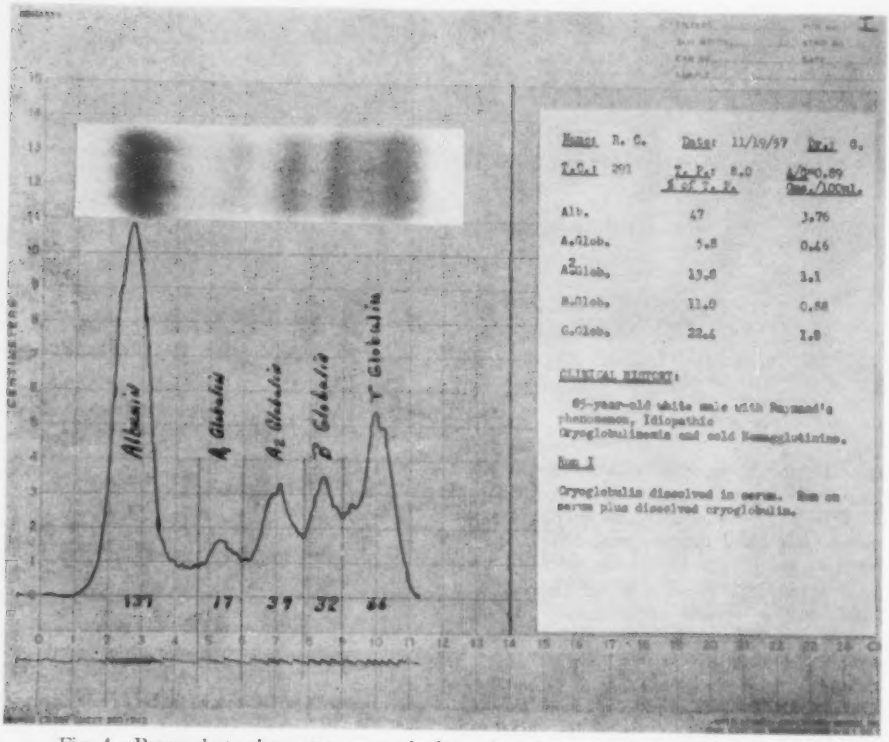


Fig. 4.—Paper electrochromatogram made from the whole serum of the patient described in the case report. There is a high normal total protein of 8 gm. The albumin fraction is slightly decreased percentwise; however, it is normal in grams per 100 ml. The alpha$_2$ and the gamma globulins show a slight increase both percentwise, and in grams per 100 ml. There is a reversal of the A/G ration to 0.89. The pattern is not specific.

normal sinus rhythm with a Grade II systolic murmur heard over the entire precordium. The abdomen was soft. The liver and spleen were not palpable. There was no abdominal tenderness. Examination of the extremities revealed a purplish-red discoloration of all the nail beds. Distal segments of the fifth finger on the right hand were blue and cold. There were areas of blotchy cyanosis over the hands as well as fingers (Figs. 1 and 2). The lobes of the ears were also cyanotic. Examination of the pulses revealed normal radial pulses and normal posterior tibial pulses. The dorsalis pedis pulses were not palpable.

Suspicion of cryoglobulinemia was first raised when blood showed immediate clotting in the needle and syringe, making it difficult to obtain blood samples without first warming the syringe. The blood studies showed a hemoglobin of 10.7 gm. and white cell count of 5950. The differential count showed 67% segmented forms, 22% lymphocytes, 10% monocytes, and 1% eosinophils. An accurate red cell count was not possible because of hemagglutination. Agglutinins were not demonstrable at 37 C. At 25 C agglutination occurred at serum dilution of 1:256. At 4 C agglutination occurred at serum dilution of 1:32,768.

Urinalysis showed a specific gravity of 1.020, with negative albumin and sugar reactions. Microscopic examination showed occasional WBC and no red cells. The serum urea nitrogen was 32 mg. %. The serological test for syphilis was negative. Total serum proteins were 7.6 gm. %, with 3.5 gm. % albumin and 4.1 gm. % globulin. Uric acid determination was 4.5 mg. %. Serum bilirubin was 0.05 mg. % direct and 0.71 mg. % total. Bone marrow examination was done by sternal aspiration and showed no evidence of increased plasma cells or the presence of myeloma or other abnormal cells (Fig. 3).

Electrophoretic patterns performed on the serum and the cold-precipitated globulin are shown in Figures 4 and 5. These demonstrate that the cryoglobulin has a mobility of gamma globulin. When the serum was cooled, a precipitate appeared in the bottom of the tube, as shown in Figure 6.

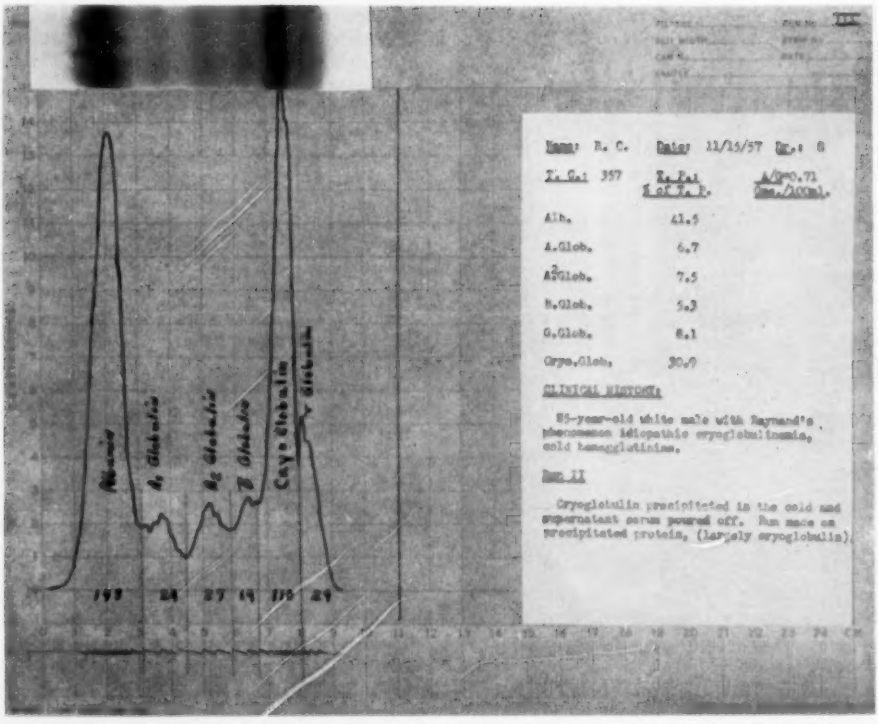


Fig. 5.—Paper electrochromatogram made on precipitated cryoglobulin after decantation of the supernatum serum. The material consists largely of cryoglobulin, although some serum still remains, and its pattern is reproduced in the tracing. Here the concentration of cryoglobulin is high, and it is seen to have the mobility of a gamma globulin.

X-ray of the chest on the fourth hospital day, when the patient had become febrile, revealed pneumonitis of the right lung (Fig. 7). The heart was in the upper limits of normal in size and was normal in contour. The aorta was slightly tortuous. X-ray of the skull showed a cranial vault of normal thickness. The pineal was calcified and in the midline. The sella was normal. There was no evidence of lesion to suggest multiple myeloma in the skull. The EKG showed changes of left ventricular hypertrophy with the pattern of left ventricular strain and/or digitalis effect.

There appeared to be variations from day to day in the amount of ischemic change present in the digits. Effort was made to keep the extremities warm by the use of heavy cotton socks and gloves. On the third hospital day, the patient became febrile, with a spiking temperature reaching 103 F. Examination of the chest revealed rales at the right base, and subsequent chest x-ray confirmed the presence of pneumonitis. Treatment with a combination of penicillin and streptomycin caused effervescence of the fever and clinical improvement. During the days in which the patient was most febrile there appeared to be some improvement in the degree of ischemia of the extremities. priscoline. Fluids were given intravenously, but tinued during this period. After the fever subsided, the patient's ischemia became progressively worse, in spite of increasing the dosage of priscoline to 50 mg. three times daily. The patient gradually became more stuporous. He developed nausea and vomiting, which persisted after withdrawal of his priscoline. Fluids were given intravenously, but his serum urea nitrogen increased and on the sixth day after admission was 64 mg. %. Although he became progressively stuporous and aphasic, there were no positive neurological findings to implicate cerebral thrombosis. He expired on the fourteenth hospital day.

Autopsy Findings.—External Examination: The autopsy was made two hours after death. The body was that of an elderly white man which measured 5 ft. 10 in. and weighed an estimated 150 pounds. There was bluish-purple discoloration of several of the finger tips and three toes on the right foot. The left eye revealed an old iridectomy scar.

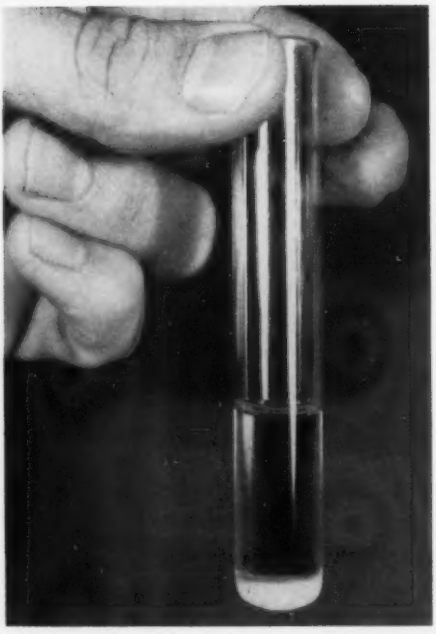
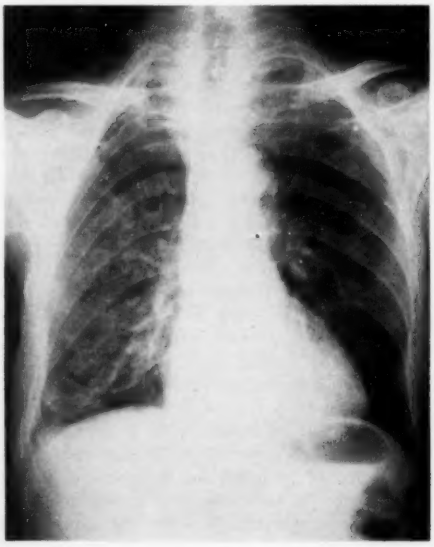


Fig. 6.—This tube of serum was cooled to 4 C. and a precipitate formed in the bottom. This was centrifuged down to form a button, and the photograph was made. The precipitate represents cryoglobulin as seen at 4 C.

Internal Examination: The aorta showed moderate arteriosclerosis with calcification. The heart weighed 380 gm. The epicardium was smooth and contained a small amount of fat. The coronary vessels showed moderate arteriosclerosis but no occlusion. The endocardial surface was smooth, but the mitral valve ring was calcified and the aortic valve showed extensive calcification with calcific aortic stenosis. No scars or infarcts were present in the myocardium. The right lung weighed 350 gm.; the left, 300 gm. Both lungs showed moderate emphysema, especially of the upper lobes. The bronchi contained frothy white fluid, and the vessels were patent. The external surfaces were grayish-brown, and on cut section a reddish-brown appearance was seen in the lower lobes, with patchy firm pale areas up to 1 cm. across, suggestive of pneumonia. The bronchial lymph nodes showed moderate edema and were black with carbon pigment. The right kidney weighed 175 gm., the left 170. Both kidneys showed moderate numbers of deep pitted scars in the cortex. One or two inclusion cysts were present in each kidney, measuring from 5 to 15 mm. in diameter, and the corticomedullary ratios were slightly reduced with associated arteriosclerosis of the renal vessels. The renal pelves appeared normal. The prostate was two time normal size, nodular, soft, and without gross evidence of cancer. The duodenum just distal to the pyloric sphincter revealed an acute ulcer in its posterior aspect. This was 15 mm. in diameter and had a gray necrotic base. The brain showed considerable arteriosclerosis of the cerebral vessels and moderate atrophy, with widening of the sulci. No evidence of infarction, hemorrhage, or tumor was found. The bone marrow of the sternum, vertebrae, and ribs showed no gross abnormalities. In the anterior superior mediastinum, occupying approximately the position of the thymus gland, was a cyst 5 cm. in diameter, which had a thin translucent wall and was filled with clear watery fluid. The remaining organs revealed no significant pathological changes.

Microscopic Examination: Sections of the heart revealed considerable arteriosclerosis with calcification of the mitral valve ring and calcific aortic stenosis. No myocardial infarcts were seen, although brown atrophy of the myocardial fibers was noted. There was acute bronchitis and acute bronchopneumonia with many segmented neutrophils in and around bronchi, especially in the lower lobes; fibrin and segmented neutrophils were also present in alveoli. The lymph nodes especially of the hili of the lungs showed edema, fluid, and segmented neutrophils in the lymphatics. The nodes also contained carbon pigment. There was arteriosclerosis and focal calcification of the renal arteries with cortical scarring and benign inclusion cysts in the kidneys. The prostate gland revealed

Fig. 7.—Chest x-ray on the fourth hospital day. It reveals a pneumonitis of the right lung. The patient was febrile at this time.



increase in the size of the acini, with moderate chronic inflammation. Sections of the large bowel contained melanin-like pigment in the lamina propria. Sections of the brain revealed cerebral arteriosclerosis with corpora amylacea in the cortex just beneath the meninges. No infarcts were found. The cyst in the mediastinum was lined with low columnar epithelium surrounded by a few lymphocytes. It exhibited no evidence of malignancy. Sections of the bone marrow revealed a slight increase in cellularity over what one would expect in an 85-year-old. However, there were normally developing cells of the granulocytic and erythrocytic series. Megakarocytes were present in normal numbers. The myeloid-erythroid ratio was 5:1, and plasma cells made up less than 3% of the total cell population. No pathologic change was recognized in the bone marrow.

Comment

Discussion of Case.—Cryoglobulinemia has been reported in patients ranging in age from 33 to 77 years, but the majority of cases have occurred during the sixth and seventh decades of life.[6] The present patient, manifesting evidence of the disorder at the age of 85, appears to be the oldest patient to be reported.

Because this patient was demonstrated to have both a large amount of cold-precipitable globulin and very high titers of cold agglutinins, it is not possible for us to state which of these conditions is largely responsible for the peripheral vascular symptoms.

In the case of cryoglobulinemia associated with cold agglutinins reported by Conn,[7] hemolytic anemia was present. Since hemolysis has been previously reported with high titers of cold agglutinins, it is logical to assume that the cold agglutinins were responsible for this manifestation. Hemolytic anemia has not been recognized in any of the cases of cryoglobulinemia not associated with cold agglutinins except for a case of chronic lymphocytic leukemia which exhibited cryoglobulins and autoimmune hemolytic disease but did not show cold agglutinins.[24] Schwartz and Jager[22] studied a case of chronic lymphatic leukemia associated with cryoglobulinemia and cold agglutinins and demonstrated that the cold agglutinins were present in the precipitable fraction. In their case, hemolytic anemia was not demonstrated, although the titer of cold agglutinins was very high. Similarly, in our case there was no definite evidence of hemolysis, even though a mild anemia was present.

The presence of changes of pneumonitis in the chest x-ray raises two questions: First, may this have been atypical pneumonia, thereby accounting for the marked elevation of cold agglutinins? Against this possibility was the apparent response to penicillin and streptomycin therapy and the postmortem demonstration of microscopic changes of bronchopneumonia rather than atypical pneumonia.

Second, are the pulmonary changes seen a result of globulin precipitation in the lungs, as has been suggested in a case reported by Barr and co-workers?[25] These workers described the presence of precipitated eosinophilic-staining material in most blood vessels of all organs of the body. This material was demonstrated to give a positive test for arginine and thus probably represented protein. The lack of evidence of ischemia or infarction of the organs made it seem more likely that the preciptitate occurred as the tissues cooled. In our case a careful examination was made of the precipitated proteins in the vessels. Precipitation of the normal proteins of the blood is consistently observed in fixed sections stained with hematoxylin and eosin. The precipitated proteins in the vessels of the present case did not appear different from those seen in cases without cryoglobulins. Agglutinated red cells are also difficult to evaluate in tissue sections, and their relationship to Raynaud's phenomena in this case remained a matter of speculation. Unfortunately, we did not have sections of the cyanotic ears or fingers. Antemortem precipitation of globulin has not been proved without doubt in the viscera other than the eyes, where retinal vein thrombosis has been noted to occur.[2]

Classification of Cryoglobulinemia.—As one studies the published literature on cry-

oglobulinemia, the complexity of this problem becomes obvious. No previous attempt has been made to classify cryoglobulinemia. In hopes that it may better our concept of this poorly understood disorder, we have suggested the classification shown in the Table. The appearance of cryoglobulin in the blood is a manifestation of an altered protein metabolism, and probably always a secondary reaction, though our current knowledge leaves us without an adequate explanation in some of these cases. Currently, we refer to this type as essential, or idiopathic, cryoglobulinemia. As our knowledge increases, this type may be removed from the classification. We have included in this classification only the more important relationships now recognized.

Essential Cryoglobulinemia: In small quantities cryoglobulins may be present without symptoms. When cold-precipitable globulins have been detected in large quantities, whether primary or secondary, most patients have demonstrated varying degrees of cold sensitivity, including urticaria, Raynaud's phenomena, acrocyanosis, and even gangrene with necrosis and ulceration.[3-11] All these manifestations have been noted in cases of essential cryoglobulinemia and, therefore, presumably are the direct result of the cold precipitable globulin. Retinal vein thrombosis and deafness are recognized manifestations of cryoglobulinemia, but other visceral lesions which have been described are of questionable significance.[2,25] Cold agglutinins have been noted in association with cryoglobulins in only two cases of the essential variety, including our case. In the previously reported case,[7] hemolysis was present.

Secondary Cryoglobulinemia: The earliest reported cases of cryoglobulinemia were secondary to other disease processes, notably multiple myeloma. About one-half of the patients demonstrating large amounts of cryoglobulins have had them in association with multiple myeloma. In approximately one-fifth of the remaining cases, the fundamental diagnosis has been chronic lymphatic leukemia. Cryoglobulins have occasionally been detected in cases of lymphosarcoma[26] and polycythemia rubra vera.[27] Large quantities of cryoglobulins were present in a case of so-called malignant reticuloendotheliosis.[28] That striking alterations in the serum globulins occur in collagen diseases has been recognized for some time, and it is not unexpected that cryoglobulins would be found in association with lupus erythematosus,[3] periarteritis nodosa,[29,30] and rheumatic fever.[31] In certain infections, notably kala azar,[32] large quantities have been demonstrated. Smaller quantities, insufficient to produce symptoms, have been detected in subacute bacterial endocarditis[32,33] and bronchiectasis.[32] In certain miscellaneous disorders, including coronary artery disease[34] and cirrhosis of the liver,[35] cryoglobulins have been demonstrated, but their significance has not been determined.

Other Dysproteinemias: The term "hyper-globulinemic purpura" was introduced by Waldenström[36] in 1943 to describe three patients with unexplained increase in serum globulin, high sedimentation rate, and purpura of many years' duration. In these patients, the serum would gel at room temperatures, but a precipitate did not form. Several cases have been reported in the European literature, and in 1954 Taylor and Battle[37] reported the first such case to be recognized in this country. The patient was observed over a period of ten years, and, in spite of the recurring episodes of purpura, the general health continued to be good. The electrophoretic pattern showed extremely high gamma globulin levels. Cryoglobulins were not detected in any of these reported cases of hyperglobulinemic purpura. Recently, Rogers and Welch[38] have reported a case of hyperglobulinemic purpura which after a benign course of over 10 years terminated in typical multiple myeloma. MacKay and co-workers[9] have reported the association of macroglobulins and cryoglobulins in the same patient. As studies on the physicochemical and immunologic nature of cryoglobulins proceed,

Classification of Cryoglobulinemia

I. Essential (idiopathic) cryoglobulinemia
  1. Asymptomatic
  2. Associated with peripheral vascular disorders
    (1) Urticaria
    (2) Raynaud's phenomena
    (3) Acrocyanosis
    (4) Gangrene
    (5) Necrosis
  3. Associated with visceral thrombosis
    (1) Retinal vein thrombosis
    (2) Deafness
    (3) Pulmonary infarction*
    (4) Cerebral purpura*
  4. Associated with cold hemagglutinins (hemolytic anemia)

II. Secondary cryoglobulinemia
  1. Neoplastic diseases
    (1) Multiple myeloma
    (2) Chronic lymphatic leukemia
    (3) Lymphosarcoma
    (4) Malignant reticuloendotheliosis
    (5) Polycythemia rubra vera
  2. Collagen diseases
    (1) Lupus erythematosus
    (2) Periarteritis nodosa
    (3) Rheumatic fever
  3. Infectious diseases
    (1) Trypanosomiasis (kala azar)
    (2) Subacute bacterial endocarditis
    (3) Bronchiectasis
  4. Miscellaneous
    (1) Coronary artery disease
    (2) Cirrhosis of liver

*See discussion in text.

these globulins may be classified on this basis. For the time being we must rely on the clinical characteristics.

Treatment of Cryoglobulinemia.—Treatment of cryoglobulinemia has been generally unsatisfactory. In secondary cryoglobulinemia, the cold-precipitable globulins may decrease when treatment to the underlying disease has been instituted. Volpe[6] has reported a limited degree of success in management of the manifestations of cryoglobulinemia when the multiple myeloma is treated with mercaptopurine, and of improvement in polycythemia vera patients after radioactive phosphorus therapy. The steroids have been of value in producing unsustained remissions in cases of idiopathic cryoglobulinemia.[4,6] Vasodilators, such as priscoline used in our case, may be useful in relieving the Raynaud's phenomena. The most promising results of treatment in essential cryoglobulinemia have been obtained with the use of bishydroxycoumarin (Dicumarol) reported by Domz and Feigin.[8] The rationale for such therapy lies in the observation by Henstell and Feinstein[39] which indicates that cryoglobulins have the ability to combine with and precipitate prothrombin and accessory factors from the blood plasma. Bishydroxycoumarin, an antiprothrombin substance, proved quite successful in the treatment of a patient reported by Domz and Feigin. Obviously, its use must be extended beyond that of one case before conclusions can be reached.

Summary

A case of cryoglobulinemia with high titers of cold agglutinins is reported in an 85-year-old white man.

Clinical manifestations include Raynaud's syndrome and acrocyanosis of the digits, nose, and ears. Central nervous system and renal impairment and pulmonary symptoms were present but may not have been related to the cyroglobulinemia and cold agglutinins.

Electrophoretic studies showed the cryoglobulin to have the mobility of a gamma globulin, as has been true in previously studied cases.

Clinical and autopsy studies showed no primary disease to account for the abnormal protein or cold agglutinins.

A clinical classification of essential and secondary cryoglobulinemia is presented, but it undoubtedly will require modification as our knowledge increases.

Memorial Hospital.

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Addison's Disease and Diabetes Insipidus

Report of a Case Secondary to Metastatic Bronchogenic Carcinoma Ten Years After Pneumonectomy

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The metastatic involvement of both adrenal glands with complete replacement by neoplasm, resulting in Addison's disease, is recognized as a most unusual if not rare occurrence.[1-6] The first well-documented cases in the American literature were reported by Butterly and his associates,[1] in 1952; Wallach and Scharfman,[2] in 1952, and Sahagian-Edwards and Holland,[3] in 1954. In 1957, Leary and Masters [5] also reported a case of Addison's disease produced by metastasis from gastric carcinoma.

Metastatic carcinoma to the pituitary gland involving both the anterior and posterior lobes and the hypothalamus, resulting in diabetes insipidus, is exceedingly rare.[6-8]

The survival of a patient 10 years after pneumonectomy for primary bronchogenic carcinoma, although not infrequently reported, remains an unusual occurrence.[10-14] In personal communications Watson [11] stated he had four cases of 10-year survival, and in one of them a second primary lung cancer developed which was nonresectable. Overholt [13] reported a five-year cure rate of 19% and a 10-year cure rate of 16% following pneumonectomy. In other statistical studies the five-year survival rates are presented as ranging from 20% to 38%,[15-18] but no figures are presented as indicative of 10-year survival rates.

It is considered of interest to add another fully documented case of adrenal insufficiency secondary to metastatic bronchogenic carcinoma to those already reported.[1-3] In none of the previously reported cases did this syndrome occur in a case of bronchogenic carcinoma that survived 10 years after pulmonary resection. Diabetes insipidus with Addison's disease secondary to metastatic bronchogenic carcinoma has never been reported.

The frequency of adrenal involvement in bronchogenic carcinoma has been reported by many observers to range from 30% to 45%.[2,3,6,19] In the report of Sahagian-Edwards and Holland,[3] there was a total of 354 cases of secondary carcinoma of the adrenal gland in 9582 autopsies. The commonest origin was the bronchus in 42%, and the female breast was next in frequency, with 34%. Bilateral adrenal metastasis occurred in 144 of the 354 cases, and, of these, 78 instances were in patients with bronchogenic carcinoma. Of the 144 cases with bilateral adrenal metastasis, 4 patients revealed recognizable adrenal insufficiency during life. In each instance the primary was bronchogenic carcinoma. Graham [19] very aptly stated that there is not even a theoretical explanation for the finding of metastasis to one or both adrenal glands at autopsy in cases of bronchogenic carcinoma.

To find cerebral metastasis in bronchogenic carcinoma is not unusual. Knights [7] found primary bronchogenic carcinoma in males and primary breast carcinoma in females to be the commonest to metastasize to the brain. Of 109 cases of pulmonary carcinoma in his report, the brain was examined in 27 cases. Cerebral metastasis was noted in 14% of the 27 cases, but no reference was made to involvement of the pituitary or the hypothalamus. Willis [6]

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quoted Simmonds, who recorded seven examples of secondary tumors of the pituitary gland, six from mammary carcinoma, and one from pulmonary carcinoma. In all of these cases the pituitary gland was normal in size, and microscopic study was essential to prove the presence of the growths. These lay in the posterior lobe, extending in some instances to the pars intermedia and stalk, but the anterior lobe was clear in all cases.

Willis also quoted another case, by Verron, in which the primary was bronchogenic carcinoma with metastatic growth replacing the stalk, posterior lobe, and pars intermedia. In his own Case 476 of bronchogenic carcinoma, a metastasis occupied the posterior lobe, whence it also invaded part of the anterior lobe.

Willis stated that metastatic growths in the pituitary gland commonly occupy the posterior lobe; deposits in the anterior lobe are exceedingly rare. By extension of the growths, the pars intermedia and stalk frequently become affected. In many of the cases symptoms of disturbed pituitary function have been present during life. This usually takes the form of diabetes insipidus with polyuria and thirst. It must be noted that diabetes insipidus may also occur with metastatic growths in the hypothalmic region and with the hypophysis intact, as reported by Futcher [8] in his case of primary bronchogenic carcinoma.

Of 100 cases of pituitary tumors reported by Rand and Rand,[9] 2 were metastatic. Of these two, one was primary bronchogenic, post resection.

The rarity of the recurrence of carcinoma in a case of 10-year survival following pneumonectomy for primary bronchogenic carcinoma, with recurrence in the stump, and Addison's disease resulting from complete replacement of both adrenal glands by the tumor, and the complete replacement of the hypophysis by metastatic tumor warrants the reporting of the following case.

Report of Case

A 58-year-old white man was admitted to St. Vincent's Hospital, New York, on April 18, 1956, because of progressive dyspnea, easy fatigue, and dizziness of six months' duration. During this time he also experienced recurrent chills and fever, low back and abdominal pain, and vomiting at irregular intervals.

Past History.—Ten years before admission a right total pneumonectomy was performed, on Sept. 24, 1946, for primary bronchogenic carcinoma originating in the right lower lobe. The microscopic report was epidermoid carcinoma. Metastasis was not present, and it was felt that all of the tumor was removed. The postoperative course was uneventful, and he was discharged on Oct. 12, 1946, as improved.

The patient was followed closely in the chest OPD of the Medical Center and by me with repeated chest x-rays. He remained in good health but for occasional upper respiratory infections and exertional dyspnea. When seen in the OPD on July 25, 1954, his status was good, and he was considered a five-year cure.

In November, 1955, he reported to the chest OPD that he had an upper respiratory infection with cough, productive of scanty white sputum, recurrent severe abdominal pain, excessive thirst, and urinary frequency.

Laboratory findings were reported as follows: The chest x-ray taken on Nov. 9, 1955, showed

Laboratory Findings

	Date					
Test	4/18/56	4/19/56	4/20/56	4/25/56	5/7/56	6/22/56
Hb., gm.	14.5					
RBC	5,100,000					
WBC	9,100					
Neutrophils,%	54					
Lymphocytes	42					
Hematocrit, mm.	44					
Urine	Neg.					
Serum						
Na, mEq/L.		139			123	
K, mEq/L.		5.3			4.6	
CL		88			98	
CL, mEq/L.		88			98	
CO_2, mEq/L.		34			28	
(vol. %)		(75)			(62)	
Serum						
Alb., gm. %			3.5			
Glob., gm. %			3.2			
Alk. Phos., B. U.			7.9	9.6		
BUN, mg. %			23		9	
Creatinine, mg. %			2.4			
Fasting blood, sugar, mg. %			87		87	
I^{131} uptake, %						2.03
ECG		Neg.				

complete opacification of the right hemithorax, with tracheal, mediastinal, and cardiac deviation into the right chest. The normal lung parenchyma on the left showed no interval change. Complete blood cell count, urinalysis, fasting blood sugar, paranasal sinus x-rays, and gastrointestinal series were all normal. The patient was thought to have psychogenic polydipsia.

On March 2, 1956, he was admitted to a municipal hospital with chills, fever, and right subcostal pain. He was treated with penicillin and discharged on March 11, 1956, improved.

On April 18, 1956, the patient was admitted to St. Vincent's Hospital because of the persistence and recurrence of his complaints since November, 1955. Severe sharp pain occurred explosively in the right upper quadrant and the right costovertebral and right loin area, associated with chills and fever that would last about 24 hours. Such an attack occurred on Feb. 25, 1956; April 13, 1956, and April 17, 1956. The pain was not related to breathing or aggravated by coughing.

Physical Examination.—The patient appeared well nourished and well developed and in no acute distress, but exertional dyspnea was evident.

The temperature was 98.4 F; pulse, 64 per minute; respirations, 20 per minute; blood pressure, 98/70 mm. Hg in both arms. The physical examination revealed pallor and puffiness of the face, arms, and hands. There was no lymphadenopathy. The trachea was retracted to the right of the midline. Right thoracotomy scar was well healed. The heart sounds were heard to the right of the sternum. The left lung was clear. The liver was at the costal arch. The lower extremities were negative. Neurological examination was within normal limits.

Chest x-ray, April 19, 1956, showed the mediastinum completely displaced into the right hemithorax. The left lung showed compensatory emphysema. Skeletal survey on April 19 showed no evidence of osseous metastasis. A gastrointestinal series on April 23 showed no abnormality.

Course.—The patient continued to complain of weakness, dizziness, and vomiting. This was particularly evident with changes in position from supine to sitting. Blood pressure recumbent was 100/70; semirecumbent, 90/70; sitting at a 90-degree angle, 80/60 and associated with severe dizziness. The rhythm at this time was regular, and the rate was 60 per minute.

Adrenal atrophy or adrenal carcinoma, primary or metastatic, was now considered.

On April 27, 1956, the following studies were performed:

1. Total quantitive eosinophil count at 9:20 a. m., 176 per cubic millimeter; 25 units of corticotropin (ACTH) was then given intramuscularly; at 2:20 p. m. the count was 220 per cubic millimeter.

2. Twenty-four-hour urine specimen revealed only 3 mg. of 17-ketosteroid.

3. Glucose tolerance test. Specimens were taken at one-half-hour intervals, with the following results:

	Mg. %	
Fasting blood sugar	= 56	Urine = 0
1	= 79	1 = 1+
2	= 113	2 = 1+
3	= 113	3 = 1+
4	= 136	4 = 1+

In view of these three studies the presence of adrenal insufficiency was believed to be established.

On May 2, 1956, deoxycorticosterone acetate in oil was given intramuscularly together with oral NaCl. He was unable to tolerate oral NaCl, and 5% dextrose in 1000 cc. of isotonic saline was given intravenously. The patient improved progressively, with blood pressure rising to 140/80 and heart rate to 60 per minute, but deoxycorticosterone acetate (Doca) was discontinued on May 12, 1956. Periorbital and pendant edema was evident. Hydrocortisone given orally was begun. At this time polydipsia and polyuria became quite evident, with fluid intake between 2900 and 6300 cc. daily and urine output ranging between 2000 and 5000 cc. Specific gravity varied between 1.000 and 1.005.

On May 19, 1956, the patient complained of double vision for the first time, but this was not confirmed on examination and cleared spontaneously. He was discharged markedly improved on May 30, 1956, with full strength. Blood pressure was 140/80; heart rate, 58 per minute. He was free of edema at this time and was maintained with hydrocortisone, 20 mg. t. i. d., and pituitary powder extract. The discharge diagnosis was (1) adrenal atrophy probably due to metastatic carcinoma and (2) bronchogenic carcinoma with left pneumonectomy, 1946.

The patient remained well until June 7, 1956, when he was distressed by persistence of double vision and recurrence of weakness. He was readmitted to St. Vincent's Hospital on June 14, 1956. On this second admission the chest x-ray revealed an increase in the prominence of the left hilar shadow and the intrapulmonary markings as compared to the previous films (Fig. 1).

Skull x-ray on June 15, 1956, revealed almost complete destruction of the posterior clinoids and dorsum sellae (Fig. 2).

EEG on June 17 was abnormal and was interpreted to indicate moderate diffuse cerebral dysfunction.

The consultant neurosurgeon concluded that a hypothalmic tumor was by far the most likely lesion; meningioma of the dorsum sella, first, and craniopharyngioma, second.

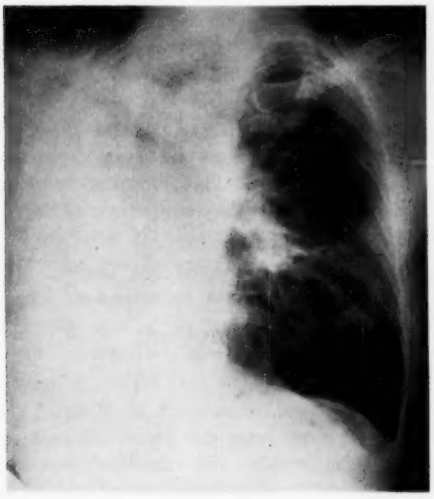


Figure 1

Figure 2

Fig. 1.—Complete opacification of right hemithorax. Increase in prominence of the left hilar shadow and the intrapulmonary markings.

Fig. 2.—Destruction of the posterior clinoids and dorsum sella.

The patient's course was progressively downhill, in spite of increased hydrocortisone administration. He went into profound shock and died on June 29, 1956.

Autopsy Report.—The following is a summary of the pertinent autopsy findings:

Chest Cavity: After the sternum was removed, the stump of the right main bronchus was seen intact but surrounded by numerous enlarged firm nodes. The right pleural cavity contained 360 cc. of dark-brown fluid. The mediastinum was shifted to the right side, and the left upper lobe extended to the midline. The mediastinum was enlarged and contained numerous large firm nodes. A few large firm nodes up to 2 cm. in diameter were noted in the supraclavicular spaces.

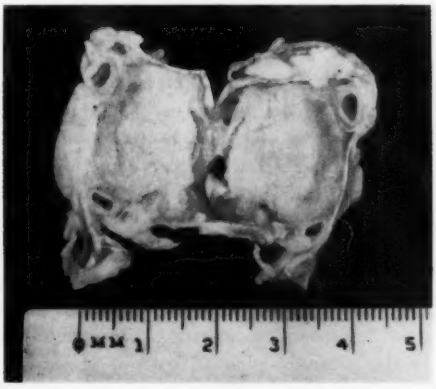
Lung: The left lung weighed 750 gm. The external surface was smooth and red-gray in color. The parenchyma was subcrepitant at the lower lobe and hyperdistended in the upper lobe. Section revealed a well-defined friable granular gray-white mass arising from the inferior main bronchus, protruding slightly into the lumen and extending into the subjacent parenchyma 3 cm. in depth.

Liver: The liver weighed 1900 gm. Numerous gray-white nodules measuring from 2.5 to 6 cm. in diameter were noted on the external surface and on section of the liver.

Adrenals: Both adrenal glands were very enlarged. They measured 9×4×2.2 cm. They were firm in consistency, and on section a grayish-white central area was noted surrounded by a fine rim,

Fig. 3.—Both adrenal glands.

Fig. 4.—The pituitary gland.



golden in color, which represented the compressed cortices (Fig. 3).

Brain: The brain weighed 1340 gm. The sella turcica was enlarged. The posterior clinoids were destroyed, and a granular prominent firm mass was noted at the site of the hypophysis, measuring 2.2×2.8×1.1 cm. (Fig. 4). Section revealed a granular grayish-white surface extending through the hypothalamus in an area 1 cm. in diameter. The cerebellum showed multiple metastasis.

Microscopic Examination.—Adrenal: The histological features were obscure. Through all elements of the cortices and medulla, there were numerous atypical epithelial cells. The lymphatic channels and blood vessels were filled with the same atypical epithelial cells. Diagnosis: Metastatic carcinoma.

Lung: The alveoli, lymphatic channels, and blood vessels were filled with clumps of atypical epithelial cells throughout the pulmonary parenchyma. There was total replacement of the epithelium of the main bronchus by atypical cells. Diagnosis: Metastatic carcinoma.

Brain: The section through the pituitary showed total replacement of the regular histological elements by atypical epithelial cells arranged in epidermoid-like structures. Diagnosis: Metastatic epidermoid carcinoma.

Comment

In the case reported the clinical history, physical examination, laboratory studies, response to therapy, and postmortem findings of the adrenal glands replaced completely by tumor confirmed the original impression of Addison's disease, yet the difficulties encountered in establishing the primary diagnosis when both the adrenal glands and the pituitary gland are simultaneously involved is attested to by the excellent discussion by Henneman [23] in a case of primary adenocarcinoma of the left adrenal gland with metastasis to the anterior and posterior lobes of the pituitary gland and the hypothalamus. In the latter case the hypophysis apparently was involved from the small cluster of metastatic cancer cells found in the lung.

The complaints of diplopia, destruction of the sella turcica, and diabetes insipidus and hypothyroidism also confirmed the presence of pan hypopituitarism, thus influencing the neurologists in considering a primary tumor of the pituitary gland. Because of the patient's rapid deterioration, it was impossible to submit him to air studies.

The cause for the adrenal insufficiency was not grossly apparent. Repeated x-rays of the chest and skeletal system failed to reveal the presence of recurrent bronchogenic carcinoma. The elevated alkaline phosphatase value was suggestive of metastatic carcinoma.

Since it was believed the patient was cured of his original bronchogenic carcinoma, the probability of a new primary bronchogenic tumor was considered. Overholt and Watson, in personal communications, referred to the work of Auerbach [21] and the report from the Mayo Clinic [22] on carcinoma in situ. In another personal communication with Auerbach he stated his own interpretation "would be that instead of recurrence of the tumor in the original bronchial stump, I would raise the question of whether it is not a second tumor arising in this area."

Auerbach et al.[21] and Ryan and McDonald [22] examined the remaining "good" lung at necropsy from males who had pneumonectomies for bronchogenic carcinoma. Definite areas of in situ carcinoma were found. It is their belief that these lesions represent new foci of malignant degeneration and not metastatic disease. These changes were more pronounced in the mainstem bronchi but were also present in the tertiary bronchi.

The pathological report of the tumor removed in 1946 and that noted at postmortem study in 1956 were both epidermoid carcinoma. The latter tumor probably could follow a new carcinoma in situ, as reported by Auerbach and his associates.[21]

Summary and Conclusions

A case of Addison's disease due to replacement by metastasis from bronchogenic carcinoma is reported.

This case report records the eighth fully documented case of Addison's disease due to complete replacement of both adrenal

glands by bronchogenic carcinoma in the American literature.

Diabetes insipidus due to the complete replacement of the pituitary gland and hypothalamus with epidermoid carcinoma secondary to a primary carcinoma of the lung is reported.

The probability of a new carcinoma resulting from a carcinoma in situ 10 years after pneumonectomy is suggested.

159 E. 49th St. (17).

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Fatal Reaction Following the Ingestion of Meprobamate

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Meprobamate (2-methyl-2-n-propyl-1,3-propanediol dicarbamate [Miltown, Equanil]) has become widely used as an ataractic or tranquilizing drug since its clinical introduction in 1955. The rarity and mildness of its side-effects, as described in early reports of clinical trials,[1,2] encouraged its liberal use in many conditions characterized by anxiety and tension. In recent months, however, numerous reports of untoward reactions to this drug have appeared in the literature. We wish to present a case which we strongly suspect of representing a fatal reaction to meprobamate.

Report of Case

A 50-year-old white housewife entered the Albert Einstein Medical Center, Northern Division, on Aug. 14, 1957, at 11:30 p. m., complaining of fever, nausea and vomiting, and a widespread erythematous rash.

Fourteen days before admission the patient had taken for the first time 2 or 3 tablets of Meprolone-2 (2 mg. of prednisolone, 200 mg. of meprobamate, and 200 mg. of dried aluminum hydroxide gel), which had been prescribed for an osteoarthritic condition. Shortly after taking these tablets she developed burning and itching under the breasts and burning of the eyes and discontinued the medication. Two days before admission she took another Meprolone tablet in the evening, and the following day she developed nausea and vomiting, and a temperature of 101 F. She took another Meprolone tablet during the day, which she probably did not retain because of vomiting. She was awakened at 3 a. m. the following morning by a burning sensation over her skin and noted an erythematous rash over the neck, trunk, thighs, and upper arms. The nausea and vomiting continued, and her temperature rose to 104 F during the day. She was seen by her local physician, who gave her tetracycline capsules. Her symptoms became severer, however, and when her usually high blood pressure was found to be 110/80 mm. Hg that evening she was sent to the hospital.

The past medical history revealed the presence for the previous three to six years of symptoms of mild angina pectoris, with some dyspnea on exertion and three-pillow orthopnea. She had had essential hypertension for three years, her blood pressures varying between 180/100 and 210/100. Six years before admission the patient had had a severe reaction to penicillin, characterized by fever and a rash, and she had never received penicillin since that time. The only recent medication she had received other than the Meprolone was reserpine (Sandril) with pyrrobutamine (Pyronil), which she had been taking for a number of months. There was no history of diabetes. An appendectomy had been performed at age 16, and a hysterectomy, at age 46.

Examination at the time of admission disclosed an obese, alert, and cooperative woman in no acute distress. Her pulse was 110; blood pressure, 110/70; respirations, 30; temperature, 100.8 F. An erythematous slightly elevated rash, with many purpuric areas, was present over the neck, chest, abdomen, inner thighs, and upper arms and over the flexor surfaces of the axillae, elbows, and groin. The head and neck were otherwise normal. The lungs and heart were normal. The abdomen was soft and nontender, with no palpable masses or organs. There was knobby swelling of several distal interphalangeal joints of the fingers. No edema of the extremities was noted. No cervical, axillary, or inguinal lymphadenopathy was present.

The laboratory data at the time of admission and throughout the course of illness are presented in the Table. An electrocardiogram was interpreted as showing diffuse myocardial abnormality associated with sinus tachycardia.

The patient was thought to be suffering from a severe drug reaction, probably due to meprobamate. She was given large doses of adrenocortical

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Laboratory Data

	Date						
	8/15	8/16	8/17	8/18	8/19	8/20	8/21
Hemoglobin, gm. %	15.5	15.6	17.5		13.1	9.8	11.6
Hematocrit, %	44	49	50		40	22	40
White cell count	18,900		28,800		41,600		
Polymorphonuclear cells, %	49						
Stab cells, %	42						
Metamyelocytes, %	6						
Lymphocytes, %	2						
Monocytes, %	1						
Blood sugar, mg. %	204	218	172		428	262	
Blood urea nitrogen, mg. %	46	75	90		130	140	
Carbon dioxide, mEq/L.			18		17	15	
Serum chloride, mEq/L.			74		67	76	
Serum sodium, mEq/L.					113	122	
Serum potassium mEq/L.			4.4		5.7	5.8	
Serum protein, gm.%		5.5				6.5	
Albumin, gm.%		3.3				3.6	
Globulin, gm.%		2.2				2.9	
Serum calcium, mg.%						9.4	
Serum phosphorus, mg.%						5.6	
Prothrombin time, %					65%		
Urinalysis							
Specific gravity	1.018		1.006		1.020		
Albumin	+1		+1		Trace		
pH	5.0		5.0		Acid		
	Many granulocytic casts				Many red blood cells		
Platelet count			116,000				
Bleeding time			1 min.				
Coagulation time			2 min. 45 sec.				
Serology	Negative						

steroids, consisting of prednisone, intravenous hydrocortisone, and intramuscular corticotropin (ACTH), together with diphenhydramine (Benadryl) and tetracycline. By the second day after admission her rash had progressed to an almost generalized purpuric and bullous dermatitis, involving especially the trunk and abdomen. Rupture of many of the bullae left large raw exuding areas on the trunk. The patient became oliguric, producing only 500 ml. of urine during a 48-hour period on the second and third hospital days. Her blood urea nitrogen rose to 75 mg. % on the second day and 90 mg. % on the third day. At this time she began to vomit moderate amounts of grossly bloody fluid. It was felt that in spite of the gastrointestinal bleeding the patient would have to continue to receive large doses of steroids, and she was given 400 mg. of cortisone and 80 units of repository corticotropin injection (ACTH Gel) intramuscularly daily for the remainder of her course.

On the third day the systolic blood pressure fell to 80-90 mm. Hg, and it appeared that the oliguria might be related to a shock-like picture. The patient did not seem to be losing large amounts of blood from the gastrointestinal tract, and her hemoglobin level had not fallen; peripheral vascular collapse, rather than blood loss, was felt to be the cause of the hypotension. She was given arterenol (norepinephrine) by intravenous infusion, and her systolic blood pressure was maintained between 100 and 150 mm. Hg. She became lethargic and mentally confused and complained of pain in the chest and abdomen. An electrocardiogram showed only frequent auricular premature contractions and a sinus tachycardia of 120.

The following day the urinary output was 900 ml., but the blood urea nitrogen continued to rise. The patient was digitalized because of persistent tachycardia and the development of slight ankle edema. On the fifth hospital day serum electrolyte studies showed a marked sodium and chloride depletion. This was partially corrected by the infusion of hypertonic saline solutions, but loss of fluid and electrolytes through the persistent vomiting and through the weeping skin lesions continued. The temperature, which had fluctuated between 101 F and 103 F, fell to 99 F, where it remained. The patient continued to be partially disoriented and began to complain of radiation of the epigastric pain to the back. A bone marrow aspiration performed at this time showed marked hypercellularity, with a myeloid-erythroid ratio of approximately 8 or 10:1. Erythropoiesis was normoblastic, and megakaryocytes were plentiful. The peripheral smears showed a marked shift to the left; stab cells, metamyelocytes, and occasional myelocytes were seen, and the neutrophils showed

toxic granulation and Doehle's inclusion bodies. Platelets were adequate. An L. E.-cell preparation was technically unsatisfactory.

Daily blood sugar values varied between 172 mg. % and 262 mg. %, except for one value on the fourth day, of 428 mg. %. Glycosuria was frequent, but the urine was never positive for acetone; insulin was given to cover the intravenous infusions.

The patient continued to vomit small amounts of blood but never developed melena. By the sixth day her hemoglobin had fallen to 9.8 gm. %, and 1000 ml. of whole blood was given. On the seventh day she developed respiratory distress and cyanosis, and coarse rales were heard throughout the chest. She died at 2 a. m., Aug. 22.

Autopsy Findings.—The autopsy was performed eight hours after death. The skin showed the severe widespread bullous and purpuric dermatitis which has been previously described. Microscopic sections of the skin revealed a necrotizing vesicular inflammation of the epidermis. In the dermis were found many areas of perivascular cellular infiltration.

The brain appeared grossly normal, weighing 1100 gm. Microscopically, there was marked perineuronal edema and neuronal shrinkage in the gray matter of the cerebrum. The blood vessels of the white matter of the cerebrum showed endothelial proliferation and perivascular cellular infiltrations. The most marked lesion in the brain was a widespread fragmentation degeneration of the granular layer of the cerebellum. The cells of the granular layer were small, distorted, and fragmented. The intercellular tissue appeared fibrillar.

The liver was large, weighed 1400 gm., and showed gross congestion; microscopic sections confirmed the impression of congestion and showed, in addition, severe and widespread fatty metamorphosis.

Areas of fat necrosis around the pancreas were noted grossly. Microscopic examination of the pancreas showed diffuse acute interstitial pancreatitis, without involvement of the acini or islets of Langerhans.

Gross study of the spleen showed the entire organ to have a peripheral shell of dark-brown firm tissue. This rim measured 1.0-1.5 cm. in thickness. Microscopic sections revealed this shell to be an extensive splenic infarction; the involved area consisted of coagulation necrosis with a sprinkling of lymphocytes.

The kidneys grossly were large, pale, and boggy, each weighing 200 gm. Examination under the microscope showed vacuolar and granular degeneration of the cells of the proximal convoluted tubules; some regenerated tubules were also seen. A proliferative glomerulitis, manifested by marked increase in the cellularity of the glomeruli, was found. The blood vessels of the kidneys revealed minimal arteriolar sclerosis and atherosclerosis of the small arteries.

There were gross petechial hemorrhages of the gastric and duodenal mucosa. Microscopy confirmed the presence of hemorrhages and showed marked congestion of the blood vessels of the stomach, duodenum, and jejunum. Sections of the colon contained several small mucosal ulcerations, with polymorphonuclear leukocytes in the ulcer bases and an overlying membrane of fibrin and debris. The distal esophageal mucosa had several areas of greenish-black discoloration. Microscopy revealed hyphae and spores having the morphology of Candida albicans in these areas, with associated necrosis and cellular infiltration.

The lungs showed extensive bronchopneumonia, pulmonary vascular congestion, and pulmonary edema. Acute bronchitis was also present.

The heart weighed 350 gm.; the left ventricle was hypertrophied, measuring 1.8 cm. in thickness. Microscopic sections showed only several minor abnormalities. There was an accumulation of large eosinophilic-staining cells with eccentric nuclei at the base of the tricuspid valve. A small proliferative lesion was found at the base of the aortic valve on the aortic surface. This area consisted of small lymphocytes and larger mononuclear cells in a loose network of fibers and areolar tissue. The coronary arteries showed minimal atherosclerosis, with no occlusion of the lumina.

The aorta contained subintimal atherosclerosis and calcification, of minimal degree. The pituitary, adrenals, thyroid, bone marrow, pelvic organs, and skeletal muscle were all normal by gross and microscopic examination.

A summary of the major postmortem findings is as follows: (1) severe generalized bullous and purpuric dermatitis; (2) marked cerebral edema; (3) cerebral vascular endothelial proliferation; (4) fragmentation degeneration of the granular layer of the cerebellum; (5) fatty metamorphosis of the liver; (6) acute interstitial pancreatitis, with moderate fat necrosis; (7) large fresh splenic infarction; (8) renal tubular degeneration; (9) proliferative glomerulitis; (10) multiple small ulcerations of the colonic mucosa; (11) congestion and small hemorrhages of the stomach and duodenum; (12) moniliasis of the esophagus; (13) extensive bronchopneumonia; (14) pulmonary congestion and edema; (15) moderate left ventricular hypertrophy.

Comment

A wide variety of side-effects and untoward reactions may occur following the use of meprobamate.[3] Drowsiness is common but often disappears following continued

treatment or reduction of the dose.[4-7] Urticarial, papular, maculopapular, purpuric, petechial, and erythematous skin lesions have been noted, usually accompanied by fever, nausea, and vomiting.[2,4-28] Severe hypotensive episodes have occurred after one or two days of meprobamate therapy.[29] Overdosage of the drug, usually with suicidal intent, has been found to cause profound central nervous system depression, similar to the effect of large doses of barbiturates.[30-34] Less common reactions have included syncope,[8-11] excitement,[6,13] gastrointestinal upsets,[2,6,7,12-14] bronchial spasm,[15] and ocular palsies with diplopia.[16] Anuria persisting for 10 days and accompanied by vertigo, vomiting, diarrhea, hypotension, and strabismus, with eventual recovery, has occurred following two months of meprobamate therapy.[35] There has been only one fatality reported, a case in which aplastic anemia developed after eight days of treatment with this drug.[36] Autopsy findings in this case revealed a hypoplastic marrow, with diffuse hemorrhages in the lungs, heart, kidneys, and abdominal muscles, with areas of infarction in the lung.

The most commonly occurring reaction to meprobamate, which most observers seem to regard as an allergic or hypersensitivity reaction, is the appearance of a rash, often within a few hours of a single 400 mg. tablet. The rash is usually erythematous and pruritic, but may be purpuric, urticarial, or maculopapular. The groin, axillae, inframammary areas, trunk, thighs, and arms are most commonly affected. Temperatures of 101 to 104 F, nausea and vomiting, pain or swelling of the joints, and hypotension often accompany the rash. A white blood cell count of 11,000 to 22,000 has been noted frequently, with an increase in the proportion of polymorphonuclear cells and an eosinophilia of 4% to 6%. In several of the reported cases in which purpura has been a common feature there have been positive capillary fragility tests, with normal platelet counts, bleeding times, and coagulation times.[10,19-22] In all reported cases the symptoms have cleared in one to seven days, either spontaneously or following treatment with antihistamines or adrenocortical steroids. In many instances the symptoms have been duplicated, after their complete remission, by the elective or accidental ingestion of another dose of meprobamate.[9,11,14,16,22-24]

The case presented above would seem to be similar in many ways to the reported cases of meprobamate reactions. The patient suffered burning and itching under the breasts shortly after her first doses of the drug. When she repeated the medication 12 days later she developed an erythematous and purpuric rash, together with fever, nausea and vomiting, hypotension, and leukocytosis. Unlike previous cases, however, in which response to antihistamines and steroids was rapid and complete, this patient became progressively more toxic, developed renal failure and gastrointestinal bleeding, and died seven days later. Postmortem examination showed a wide variety of lesions, including evidence of necrosis in the skin and spleen; degenerative changes in the cerebellum, liver, and renal tubules; inflammatory reactions in the pancreas, lungs, and colon, and vascular lesions in the cerebrum, dermis, and gastrointestinal mucosa.

A number of autopsy findings in this case are suggestive of a toxic reaction to a drug or other exogenous substance. The widespread fragmentation degeneration of the granular layer of the cerebellum has been cited by Neuberger in chronic alcoholism.[37] Endothelial proliferation of the cerebral vasculature,[38] renal tubular and glomerular lesions,[39] and fatty metamorphosis of the liver [40] are also common findings in drug toxicity. The presence of purpuric skin lesions as well as petechial and hemorrhagic areas of the gastrointestinal mucosa is of interest in view of the reports of nonthrombocytopenic purpura following meprobamate ingestion.[17-20] The bronchopneumonia, moniliasis, and interstitial pancreatitis probably represent terminal changes,

although the possibility that the latter lesion may be related to adrenocortical steroid therapy is suggested by a recent report of Carone and Liebow.[41]

Since the onset of this patient's symptoms seems related to the ingestion of Meprolone-2, a tablet containing prednisolone as well as meprobamate, both of these drugs must be considered as possible causes of her illness. There are several reports of erythematous, maculopapular, ecchymotic, and purpuric skin reactions following the use of prednisone and prednisolone.[42-44] However, these reactions occurred after at least 17 days (average time, 3 months) of daily treatment with prednisone and were not accompanied by any other symptoms suggestive of an allergic reaction. The similarity of this patient's early signs and symptoms to those described in previous cases of meprobamate reactions would seem to point to this drug as the more likely offender.

Summary

A case is presented of severe purpuric and bullous dermatitis, accompanied by widespread systemic involvement, and terminating in death. This illness occurred shortly after the ingestion of several tablets of Meprolone-2 (2 mg. of prednisolone, 200 mg. of meprobamate, and 200 mg. of dried aluminum hydroxide gel). For reasons discussed above, we feel that this case very likely represents a fatal reaction to meprobamate.

Dr. Henry Brody reviewed the pathologic findings in this case.

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CORRECTION

In the article "Primary Aldosteronism with Diabetes Mellitus," by Drs. Richard C. Sorce and William E. Whitstone, in the July issue (p. 131), the address of the authors was omitted. Their address for procurement of reprints is St. Joseph's Hospital, 2117 E. Carson St., Pittsburgh 3, Pa.

Evolution of Modern Medicine

The History of Cellular Hypersensitivity

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The recognition of allergic states came early in the history of recorded medicine, as evidenced by Hippocrates, Lucretius, Galen, and the Babylonian Talmud. Yet the foundation of investigative work rests in the monumental paper of an Englishman, Charles Harrison Blackley, "Experimental Researches on the Causes and Nature of Catarrhus æstivus (Hay-Fever or Hay-Asthma)," 1873. These important observations were shelved for 30 years, until Dunbar, in 1905, corroborated Blackley's findings.

When Bostock wrote his classical description of hay fever, in 1819, he stated his belief that in his own case it was not caused by the effluvium of grass or hay. This he reaffirmed in 1828 after further study for a second publication. Elliotson, in 1830, disagreed and stated, "I do not believe it depends upon any other part of the grass than the flower." He also described the hay fever case of a lady: ". . . that on handling the flowers of grass her hands always became instantly inflamed. It [hay-fever] would appear, too, to run in families. This lady thought it was the pollen." Morrill Wyman, of Cambridge, Mass. (1854-1872), also made noteworthy contributions on the subject of hay fever and recognized ragweed pollen as a causative agent.

Amid increasing confusion concerning etiology, Blackley undertook to prove experimentally the relation between hay fever and pollen. "During the summer of 1865 as much pollen as could be obtained from two anthers of the Lolium Italicum was applied to the center of the anterior surface of one forearm after the skin had been abraded as in the ordinary mode of vaccinating." He stated, "I have, at times, thought that the continued contact with pollen had a tendency to create a certain degree of tolerance for it." After altitude studies, "we have also seen that pollen rises to high altitudes, and is carried very long distances by atmospheric currents." Concerning symptoms, "the disease seems to affect persons of all temperaments and all kinds of constitutions but if there is one temperament which, more than another, predisposes to attacks of hay fever it is the nervous temperament."

The school of bacterial allergy held sway until the turn of the century, when new evidence was presented. The attempt, which was destined to failure, of Dunbar (1905) to develop an effective antitoxin (Pollantin) after injecting cereal-grain pollens into horses had been the outgrowth of the work of Sewall (1882-1889). Henry Sewall immunized pigeons against rattlesnake venom, thus laying the groundwork for the production of antivenom by Calmette and diphtheria antitoxin by von Behring (1893). Richet, and his associates Hericourt and Portier (1902), using the toxic substance of a stinging nettle, found that reinjection after an incubation period of approximately 10 days was often followed by a severe or fatal reaction in the experimental animal. He felt that the body lost some protective mechanism, and so coined the word "anaphylaxis" to describe the violent reaction of dogs following a second dose of extract from sea anemones.

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Arthus, in 1903, observed the reaction of sensitized rabbits to subcutaneous injections with specific protein, leading to the use of the term "Arthus phenomenon." A significant contribution of Arthus was the demonstration that a nontoxic substance like dog serum could cause an "anaphylaxis." Studies on the incubation times of artificially acquired sensitivity by Clemens von Pirquet (1903-1905), a Viennese physician, produced his theory of "altered reactivity," or "allergy." In their monograph, von Pirquet and Schick comment, "there exists a casual connection between the formation of antibodies and disease, whereby we stress the point that we do not identify the term antibody with precipitin." Von Pirquet extended his theory to include the mechanism of the defense of an organism against infectious germs, stating: "This ability to localize a repeated infection does not rest on the presence of free antibodies in the body fluid but upon a property of the cells acquired through the first disease. We see in it an expression of cellular immunity." He goes on further: "Besides hypersensitiveness there is another principle known, namely the transition of this hypersensitiveness to lack of sensitiveness—Immunity."

At this time (1906), Alfred Wolff-Eisner, of Berlin, wrote of drug idiosyncrasy as a form of anaphylaxis. In Boston, Theobald Smith described the phenomena of serum sensitivity following diphtheria antitoxin injection. Confusion meanwhile arose in the meaning of the words allergy, immunity, and anaphylaxis, owing to differences between the "natural" phenomenon of sensitivity in man and the artificially induced sensitivity in animals. The unsettled controversy about the role of histamine in anaphylactic shock had its beginning with the paper by Dale and Laidlaw (1910) on histamine shock. The numerous blood changes which were unexplained by histamine release and the inability to find measurable quantities of blood histamine were objections to the acceptance of the theory that histamine damaged the cells. Simutaneous with the work of Otto (1906), who measured serum antibodies in passively sensitized guinea pigs, Besradka and Rosenau developed the idea of hyposensitization, the foundation of future injection therapy, and Rosenau and Anderson worked out many of the concepts of anaphylaxis. They described antianaphylaxis following repeated small injections of antigen and showed that sensitization could be transferred in utero from mother to offspring.

The studies of I. Chandler Walker, Rackemann, and Schloss on skin testing and the numerous reports of successful treatment with extracts between 1915-1920 established these procedures and hastened the acceptance of the allergic nature of hay fever and bronchial asthma. In *The Lancet* of 1911, the experimental evidence from L. Noon's lab was "that the sensitivity of hayfever patients may be decreased by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations only serve to increase the sensitivity." The most important discovery of the phenomenon of passive transfer, by Prausnitz and Kustner, in 1921, stimulated great interest in the subject of immunology and led to the significant work of Coca and his associates with atopic reagins. Coca used the word reagin to describe the skin-sensitizing antibody of man which was found to be thermolabile, loosely attached to antigen, and not identified by precipitin or complement-fixation tests and which would not cause contraction of nonstriped muscle.

Although much progress had been made in experimental production and treatment of hypersensitivity states, the interrelation between immunity and anaphylaxis remained unsettled. Henry M. Ray, in 1924, stated, "anaphylaxis and immunity are but different phases of the same phenomenon; both processes have in common a purposeful attempt to protect." He said, "anaphylactic response is dependent not on hypersensitiveness but really an expression of an increased protective reaction (immunity)." However, these

thoughts originated as early as 1907, when Victor C. Vaughan, suggested that immunity and anaphylaxis were expressions of an identical mechanism. In 1926, Levine and Coca further clarified the situation by studies proving that clinical protection from pollen injections was not due to neutralization of sensitizing antibodies but to formation of neutralizing immune antibodies. These facts were supported by Cooke (1935-1937) and Loveless (1942).

Other significant contributors have been Meltzer (1910), who found correlation between bronchial asthma and anaphylaxis in guinea pigs; Duke (1925), who described physical allergy, and Warren T. Vaughan (1930), who wrote on food allergens and allergic migraine. Certainly this paper would be without a point not to mention the evidence presented by Arnold Rich (1942) that the vascular lesions of periarteritis nodosa in five cases coming to autopsy were demonstrative of the anaphylactic type of hypersensitivity following the clinical use of foreign serum or sulfonamides.

Summary

This is a perusal of cellular hypersensitivity in its infancy. Let us hope that its growth will be more readily accepted and encouraged by physicians and laymen alike.

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Contributions of Basic Science to Modern Medicine

A Recently Recognized Pathway for Glucose Catabolism—Pentose Phosphate Pathway

STANLEY J. WOLFE, M.D., San Francisco

Progress in biological chemistry during the past few decades has led to better understanding of many problems in clinical medicine. Only rather recently it became apparent that pathways other than the classical Embden-Meyerhof (anaerobic glycolysis) are operative in glucose catabolism by mammalian tissues. Following the pioneer investigations of Warburg, Lipmann, and Dickens, and recently those of Horecker, Racker, and others, the existence of an alternate pathway for glucose catabolism has been recognized. This schema has been called the hexose monophosphate shunt, the glucose oxidative pathway, or the pentose phosphate pathway and involves a series of reactions in which phosphorylated sugars with three, four, five, six, and seven carbon atoms (triose, tetrose, pentose, hexose, and heptose phosphates) occur as substrates and intermediates.

Recognition of this catabolic route has stimulated investigation into its possible role in both normal and abnormal mammalian metabolism. The purpose of this paper is to outline briefly the biochemistry of the pentose phosphate pathway as it is now understood and to summarize aspects of interest and importance to the clinician.

Biochemical Considerations

1. *Embden-Meyerhof Pathway.*—A major ultimate fate of glucose is the break-down of the hexose (six carbons) molecule first to three-carbon acids, pyruvic and lactic acids, which in turn are oxidized to CO_2 and H_2O as final chemical products. The term glycolysis has been applied to the processes by which glucose is broken down to lactic acid, a series of reactions commonly associated with the names of Embden and Meyerhof. In the course of these reactions no oxygen is consumed and there is a net production of chemical energy. The subsequent oxidation of lactic and pyruvic acids to CO_2 and H_2O results in the production of even greater energy.

2. *Pentose Phosphate Pathway.*[1,2]—This recently recognized mode of glucose utilization differs from the glycolytic pathway in that oxidation occurs early in the sequence. The first reaction is phosphorylation of glucose to glucose-6-phosphate, which, in turn, is oxidized to 6-phosphogluconate by the removal of hydrogen. The latter reaction requires the enzyme glucose-6-phosphate dehydrogenase and the co-factor triphosphopyridine nucleotide (TPN) (Fig. 1). This

Figure 1

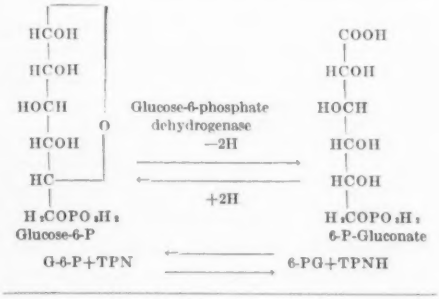

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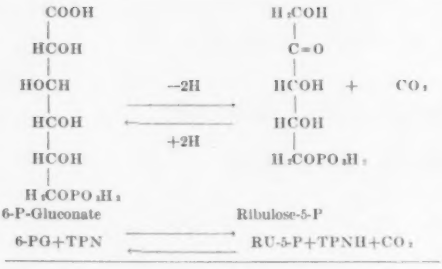
Figure 2



type of oxidation consists of a transfer of a hydrogen atom to the coenzyme (TPN), resulting in the formation of TPNH or reduced triphosphopyridine nucleotide. TPNH is an important coenzyme for reactions in which metabolites are reduced—giving up a hydrogen atom to the metabolite, with resultant regeneration of TPN, which is then available again as an oxidative coenzyme.

6-Phosphogluconate is oxidized to the pentose, ribulose-5-phosphate, with formation of CO_2 (Fig. 2). Again TPN is a co-factor and TPNH is generated.

The subsequent reactions of the pentose phosphate pathway are all nonoxidative. In the next one, the transketolase reaction, the active glycolaldehyde $\left(\begin{array}{l} H_2COH \\ | \\ C{=}O \\ | \end{array}\right)$ of xylulose-5-phosphate, converted from ribulose-5-phosphate generated in the preceding reaction, condenses with ribose-5-phosphate, the isomer of ribulose-5-phosphate. The products are a seven-carbon sugar, sedoheptulose-7-phosphate, and glyceraldehyde-3-phosphate (Fig. 3). The enzyme transketolase and co-factor thiamine pyrophosphate are required.

In the next reaction catalyzed by transaldolase, sedoheptulose-7-phosphate and glyceraldehyde-3-phosphate are converted to fructose-6-phosphate, a six-carbon sugar, and erythrose-4-phosphate (Fig. 4).

Fructose-6-phosphate, an intermediate in the Embden-Meyerhof pathway, links the alternate and classical routes. Another common intermediate is glyceraldehyde-3-phosphate.

Erythrose-4-phosphate may also enter into a transketolase reaction, accepting the active glycolaldehyde of xylulose-5-phosphate to

Figure 3

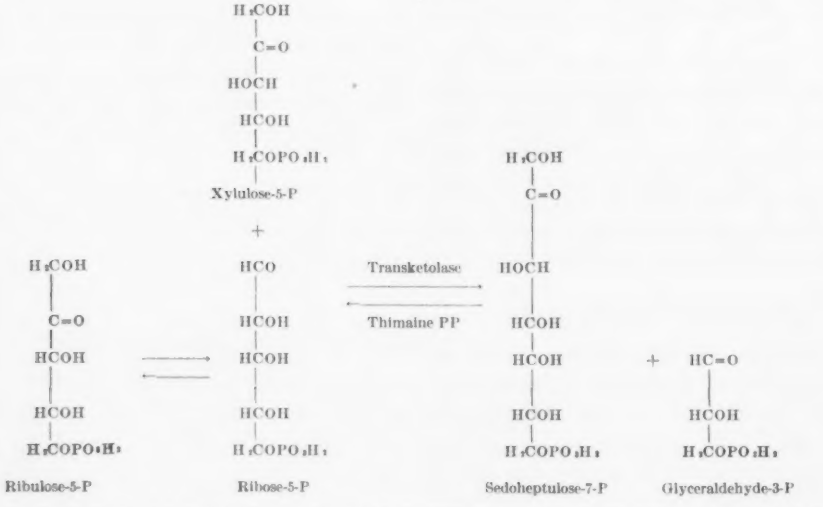


Figure 4

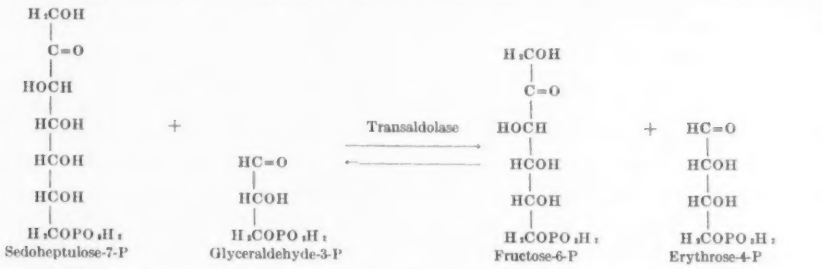


Figure 5

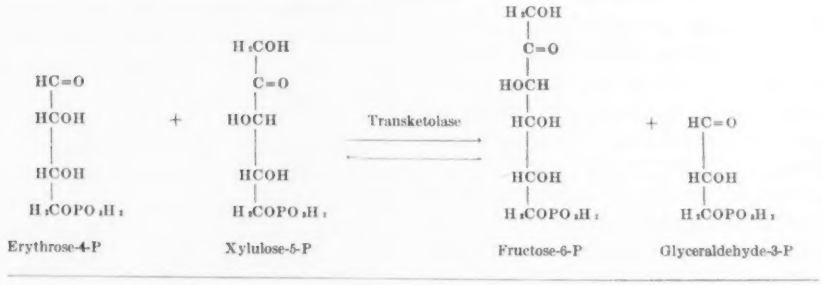
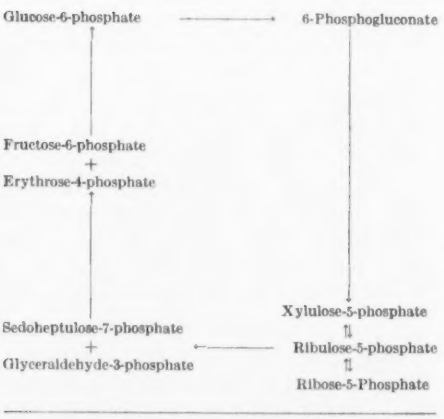


Figure 6



form fructose-6-phosphate and glyceraldehyde-3-phosphate (Fig. 5).

Fructose-6-phosphate may be converted to glucose-6-phosphate by the enzyme isomerase, establishing the cyclic nature of the shunt (Fig. 6).

It can be demonstrated that for every three glucose molecules phosphorylated by ATP three molecules of carbon dioxide are formed, two molecules of glucose-6-phosphate are regenerated, and one molecule of triose phosphate appears, which may enter the Embden-Meyerhof cycle or be reconverted to hexose.

3. *Assay of the Pathways.*—Since the carbon atoms of glucose have different fates in the two pathways, utilization of C^{14}-labeled compounds has made possible their separation. In the glycolytic pathway, hexose is converted to two molecules of pyruvate in such a fashion that Carbons 1 and 6 of glucose give rise to the same carbon atoms of pyruvate. In the subsequent oxidation of pyruvate to CO_2, radioactivity originally in Carbons 1 and 6 of the original hexose appears in CO_2 at an equal rate. In the pentose phosphate pathway, CO_2 arises from Carbon 1 of glucose, while Carbons 2 to 6 are converted to pentose. Therefore,

radioactivity from Carbon 1 appears as radioactive CO_2 at a considerably faster rate than from Carbon 6, as compared to the approximately equal rates of appearance of Carbons 1 and 6 when the Embden-Meyerhof pathway is operative. Application of complex mathematical formulae to these theoretical concepts has permitted assessment of the relative magnitudes of the two pathways in a variety of tissues, utilizing as substrate glucose labeled with radioactive carbon (C^{14}) on one or another of its carbon atoms.

Clinical Considerations

The presence of interfering oxidative mechanisms has complicated assessment of the magnitude of the pentose phosphate pathway, but investigations have indicated its activity in a variety of animal tissues, including rat liver, kidney, and spleen. It also occurs in cells of several types of neoplastic tissue but is apparently absent from brain, heart, and skeletal muscle. Most studies have involved isolated tissues, and pentose phosphate activity is much less readily demonstrated in vivo. In a few instances, however, recognition of the alternate pathway has lead to clearer understanding of clinical problems. The mechanism of ketosis associated with deranged glucose metabolism in diabetes mellitus may be related to a disorder of the oxidative reactions of the pathway. Several drug-induced hemolytic anemias have been shown to affect erythrocytes lacking one of the enzymes of an oxidative reaction. The mechanism of action of methylene blue in controlling methemoglobinemia has been explained in terms of the pathway as it occurs in erythrocytes, and the enhancement of erythrocyte preservation by addition of purine nucleotides to the anticoagulant has also been so explained. Finally, dietary deficiency of thiamine, the phosphorylated form of which is a co-factor in one of the reactions, has been shown to influence the pathway in human erythrocytes. These matters will now be enlarged upon.

Diabetes Mellitus.—The possibility that the pentose phosphate pathway has a role in the development of some of the aberrations observed in diabetes mellitus has been explored.[3] Homogenates of normal and diabetic rat livers require TPNH for (or at least it limits the rate of) cholesterol synthesis, and fatty acid synthesis is enhanced by TPNH. It was concluded that in diabetes, a block in fatty acid synthesis occurs at the site of action of TPNH—at the reduction of crotonyl-CoA (coenzyme A) to butyryl-CoA. TPNH is a product of the first two oxidative steps of the pentose phosphate pathway (Figs. 1 and 2) but not of the Embden-Meyerhof, and a possible link between abnormal diabetic metabolism and the more recently recognized pathway is thus suggested. In intact animals, diabetic acidosis is accompanied by accumulation of β-hydroxybutyric and acetoacetic acids. The CoA derivatives of these ketone bodies are the two fatty acid precursors preceding the step shown to require TPNH produced in the oxidative steps of the pathway.

Erythrocytes.[4]—Although mature nonnucleated mammalian erythrocytes catabolize glucose in vitro principally to lactic acid by the anaerobic-glyclolytic pathway, most of the enzymes of the pentose phosphate pathway are present in these cells. The erythrocyte is an ideal tissue for studying the relative magnitude of each route, since there are no other interfering oxidative reactions (Krebs' cycle) and any CO_2 generated is assumed to arise from the pentose phosphate pathway. Moreover, the erythrocyte is a most readily available tissue in which to study human cellular metabolism.

There is ordinarily a very low level of glucose oxidation in mature mammalian eryhrocytes, but it has been known for many years that it could be stimulated manyfold if the incubation were carried out in the presence of methylene blue, certain other dyes,[5] or tissue extracts.[6] Indeed, the earliest demonstrations of the oxidative reactions of the pentose phosphate pathway were derived from studies with red cells and methylene

blue. Recently the cyclic nature of the pathway was demonstrated in methylene blue-stimulated erythrocytes with use of radiocarbon techniques. It was shown that intact erythrocytes have the enzyme potential to recycle 5-carbon fragments (pentose) to glucose-6-phosphate [7] (Figs. 3, 4, 5, and 6) but not in themselves to oxidize glucose-6-phosphate to pentose and CO_2. Methylene blue, other dyes, and tissue extracts, by virtue of their ability to carry electrons directly to oxygen and presumably substituting for enzymes that are lacking in non-nucleated erythrocytes, provide the mechanism for initiating glucose oxidation and permitting the pentose phosphate pathway to recycle in these cells.

Thiamine Deficiency.—As noted in Figure 3, thiamine pyrophosphate is a co-factor for the transketolase reaction. Recent studies indicate that erythrocytes of thiamine-deficient rats exhibit impairment of this reaction which can be reversed by administration of thiamine in vivo or in vitro.[8] A profound depression of the transketolase reaction also occurs in erythrocytes of rats treated with the thiamine antagonist oxythiamine.[9]

These observations have been extended to human thiamine deficiency and evidence of the same alteration in human erythrocytes has been found.[10] To date the defect has been noted only in subjects with Wernicke's encephalopathy exhibiting ophthalmoplegia. In this country Wernicke's encephalopathy occurs almost exclusively in alcoholics who have subsisted on grossly deficient diets for long periods. It is manifested by weakness or paralysis of the lateral rectus muscles of the eyes supplied by the sixth cranial nerve, and occasionally the third nerve is also involved. In addition, nystagmus, ataxia, and peripheral neuritis are usually exhibited. It has been demonstrated that that extraocular muscle weakness of Wernicke's encephalopathy is not affected by bed rest, alcohol withdrawal, and administration of a purified diet containing ascorbic acid and all of the B-vitamins other than thiamine but that when thiamine alone is added to the purified diet rapid clearing of the ophthalmoplegia ensues. Erythrocytes of subjects (chronic alcoholics) with the other abnormalities usually attributed to thiamine deficiency—nystagmus, ataxia, peripheral neuritis—but in the absence of ophthalmoplegia have shown no evidence of a defective transketolase reaction. In subjects with ophthalmoplegia, treatment with thiamine promptly relieved the eye signs, and a slow but definite return to normal erythrocyte metabolism was observed. Thus, recognition of the pentose phosphate pathway in erythrocyte metabolism has evolved into a method that permits demonstration of thiamine deficiency in a readily accessible mammalian tissue.

Methemoglobinemia.[4,11]—The iron of hemoglobin is normally in the ferrous (reduced) state and in its function as an oxygen carrier is oxygenated and deoxygenated without change in valence. In methemoglobinemia iron has been oxidized from the ferrous to the ferric form, but the change is easily reversible and does not cause red cell destruction. Methemoglobin is unable to transport oxygen, and when enough (20% or more) accumulates in the blood symptoms ascribable to hypoxia may result. In hemolysates hemoglobin is rapidly auto-oxidized to its ferric form (methemoglobin), indicating that the intact erythrocyte possesses some mechanism for preventing this and maintaining hemoglobin in the reduced state.

Methemoglobinemia may occur as a rare familial disease in which normal reduction of methemoglobin appears to be at fault. More commonly, methemoglobinemia results from exposure to certain drugs which preferentially oxidize hemoglobin and overcome the normal red cell-reducing mechanism. Nitrites, sulfonamides, and aniline derivatives are the most important agents in producing this condition.

Methylene blue has been effective in controlling primary methemoglobinemia and in reversing the drug-induced type. Years ago it was shown that methylene blue alone would convert hemoglobin to methemoglobin

but that on addition of glucose this was reversed. The substrate for the reaction was glucose-6-phosphate, which was oxidized to 6-phosphogluconate by glucose-6-phosphate dehydrogenase and TPN (Fig. 1). It is now evident that methylene blue does not convert methemoglobin to hemoglobin by its own reductive capacity but through acceleration of the normal erythrocyte conversion mechanism which requires TPNH produced by Steps 2 and 3 of the pentose phosphate pathway.

In primary methemoglobinemia there is apparently absence of a red cell co-factor, methemoglobin reductase, essential to the normal reducing mechanism. Methylene blue coupled with TPNH substitutes for this cofactor.

Primaquine Sensitivity.—Primaquine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, is an effective and widely used antimalarial agent. However, it induces intravascular hemolysis in 10% of Negroes, although rarely in caucasians. This phenomenon is due to an intracorpuscular defect [11] and is a function of cell age (tendency to hemolyze increases with age of cell). The defect is not a manifestation of any previously described red cell abnormality, and there is no alteration in fragility to chemical, osmotic, and mechanical lysis; electrophorectic mobility; susceptibility to alkali denaturation; antigenic pattern, or reaction to Coombs test. The erythrocytes of susceptible persons have a low reduced glutathione (GSH) concentration and an increased tendency to form Heinz bodies. In addition to primaquine, hemolysis can be induced by other analine derivatives, including acetanilid, sulfanilamide, thiazolsulfone (Promizole), phenylhydrazine, sulfoxone (Diasone), and acetophenetidin (phenacetin).[12-18]

The basic defect in sensitive red cells is thought to be deficiency of glucose-6-phosphate dehydrogenase activity [19] (Fig. 1). As a result of this enzyme deficiency there is failure of generation of TPNH, which is required to maintain normal intracorpuscular concentrations of GSH, which is oxidized by the aniline derivatives:

$$2GSH + TPN \rightleftharpoons GSSG + TPNH$$

(GSSG: oxidized glutathione)

It has been recently proposed that incubation of cells with primaquine or similar agents results in oxidation of GSH. In normal cells the GSSG formed is reduced rapidly to GSH through the action of TPNH produced when glucose-6-phosphate and 6-phosphogluconate are oxidized. In sensitive cells TPN reduction to TPNH is decreased because the deficiency of the enzyme glucose-6-phosphate dehydrogenase prevents oxidation of glucose-6-phosphate, which in turn restricts the amount of phosphogluconate available for further oxidation (Figs. 1 and 2). The role of GSH in the economy of the erythrocytes is as yet unknown.[20]

A similar reduction in erythrocyte GSH has been demonstrated in examples of hemolytic anemia caused by nitrofurantoin [21] and favism,[22] although it is not yet clear that a deficiency of glucose-6-phosphate dehydrogenase is the basic defect.

Erythrocyte Preservation.[23]—When whole blood is stored in acid-citrate-dextrose medium the plasma components are quite stable but the erythrocytes begin to deteriorate within a few days and exhibit physical and chemical changes known as a "storage lesion." These changes include the decreased ability to metabolize glucose, the loss of K^+ from within the cells and corresponding replacement by Na^+, increased osmotic and mechanical fragility, and the decreased ability of the cells to survive when transfused into a recipient. A corresponding decline in certain high energy phosphate compounds (ATP) also occurs. Since ATP is essential for phosphorylation of glucose to glucose-6-phosphate, the metabolic activity of the cell declines and a loss of cell viability follows.

The purine nucleosides, adenosine and inosine, have been shown to preserve the physical and chemical characteristics of erythrocytes during storage and approxi-

mately double the permitted storage time over that of blood collected in ordinary acid-citrate-dextrose medium. It has been suggested that in the erythrocyte adenosine is converted to inosine, which is split to ribose-1-phosphate, which, in turn, is converted through an isomerase to ribose-5-phosphate. Ribose-5-phosphate is an important substrate in the pentose phosphate pathway (Fig. 3) and thus participates in energy-yielding reactions to maintain the cell. It has been further suggested that the protective effect of glucose, adenosine, and inosine on stored erythrocytes may be related, in part at least, to the ability of these substances to maintain the reduced glutathione concentration of the cells (see above).[24]

Summary

An alternate pathway of glucose metabolism has been recently recognized in which oxidation occurs early in the sequence, yielding pentose-phosphate and carbon dioxide. This is in contrast to "classical" anaerobic glycolysis in which glucose is split to the three-carbon acids, lactic and pyruvic acid, which in turn may be oxidized to carbon dioxide and water.

The role of the pentose phosphate pathway in mammalian metabolism has not been defined, although the enzymes required for the newer pathway are present in many animal tissues. Mammalian erythrocytes contain most of these enzymes and lack interfering oxidative reactions (Kreb's cycle), and a number of clinical problems involving erythrocytes—drug-induced hemolytic anemias, methemoglobinemia, and erythrocyte preservation—have been clarified in terms of the pathway. Erythrocytes may also provide a means of studying thiamine metabolism, since one of the reactions of the pathway is thiamine-dependent.

A possible relationship to abnormal metabolism observed in diabetes mellitus is reviewed.

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News and Comment

ANNOUNCEMENTS

Meeting of Academy of Psychosomatic Medicine.—The fifth Annual Meeting of The Academy of Psychosomatic Medicine will be held Oct. 9-11, 1958, at the Park Sheraton Hotel, New York City. The program will be devoted to "The Psychosomatic Aspects of Internal Medicine" and will include formal papers, panel discussions, and luncheon conferences. The meeting will be open to all scientific disciplines, as well as psychologists, social workers, and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 E. Washington St., Chicago 2.

Doctors in good standing in their county medical society and clinical psychologists with degree of Ph.D. are eligible to join the Academy.

Books

EDITED BY WILLIAM B. BEAN, M.D.*

Natural Magick. By John Baptista Porta. Price, $7.50, boxed. Pp. 409, with many illustrations. Basic Books, Inc., Publishers, 59 4th Ave., New York 3, 1957.

Basic Books has done contemporary science, physicians, and historians a handsome favor by bringing out John Baptista Porta's book on "Natural Magick," a facsimile reprint of the London Edition of 1658. It is one of the Collectors Series in Science, edited by Derek Price. Among scientists, at least, "science" is accepted as a satisfactory, indeed an essential, state of mind. How did science get that way? How did it begin? It is difficult to visualize the hodgepodge of fact, fantasy, and pure fabrication which was subscribed to and endorsed by the most learned men three hundred years ago, when science was providing the impetus under which the age-old belief in natural magic was starting to crack. Man's fallibility and gullibility are old stories, old and new. Unhappily today some masquerading as scientists cannot separate the chaff from the chaffers. In this copy of an edition with handset type and all the quaint irregularities of letters and line, the f's hard to tell from s's, at least for me, there is a conglomerate but not a homogenate of froth, sediment, and good clear water. Porta properly begins with the definition of magic. It follows: "There are two sorts of magic: one is infamous, and unhappie, because it has to do with foul spirits, and consists of Inchantments and wicked Curiosity; and this is called Sorcery; an art which all learned and good men detest; neither is it able to yield any truth of Reason or Nature, but stands merely upon fancies and imaginations, such as vanish presently away, and leave nothing behinde them; as Jamblichus writes in his book concerning the mysteries of the Aegyptians. The other Magic is natural; which all excellent wise men to admit and embrace, and worship with great applause; neither is there anything more esteemed, or better thought of, by men of learning."

The savor of antiquity, the bibliophile's pleasure in the feel and smell of dusty old volumes, is one remove from our fingertips in this handsome book. But we love it, for here is an example of the tangled knots of fact, fancy, and fiction which made up natural history or natural philosophy in the days when the first gleamings of scientific thought were easily apparent, though not yet strong and lusty. All its traces remain today. In "Natural Magick" we see the clear precursors of our latter-day heresies. Half the charm of this book is the enthusiastic wonder with which nature is confronted by these children of nature living in the glow of the Renaissance. Burning curiosity and delight in natural things, now so quickly lost by our children in an other-directed culture, gave yeasty excitement and gusto to life. When conformity rather than curiosity becomes the impelling drive, a powerful search for ephemeral and illusory security displaces wonder and curiosity. This unhappily is the mark of *our* time, midcentury U. S. A.

Each chapter in this volume is an essay in itself. Different ones illustrate the radically different levels of objectivity current three or four hundred years ago. The first version of Porta's book, published in Naples a hundred years before the English edition reviewed here, was an elaboration of the minutes of the first scientific society in the world, the get-togethers of the charmingly naive men of

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

Renaissance Italy who called temselves the *Otiosi*, men of leisure. They had regular meetings in the homes of the members, discussed "science," performed experiments, related their own do-it-yourself investigations, and shared ideas in a group obviously modeled on the flourishing literary clubs of that day. It was a forerunner of scientific societies such as the accademia dei Lincei 1600, the accademia del Cimento 1657, and the Royal Society of London. The close intermingling of magic and mischief in this brief garden-of-Eden phase of science quickly brought trouble to the Otiosi. Porta was accused of dabbling in black magic and dealing with the occult. He was denounced by Pope Paul V. Luckily and surprisingly, Porta was just scolded but not seared in the cannabalistic inquisitional fires of the day. Somehow he was able to establish his point, for even as he said, he *was* actually a seeker after truth rather than a necromancer "an evoker of incubi and succubi." As one with "pull," he survived. Dozens died. But science survived, and from such small beginnings we now have learned how to spend billions of dollars a year on science.

According to the best evidence the first edition of this book was printed when de la Porta was nearly twenty-two years of age. He was a genius and a child prodigy, and he covered a lot of ground. In addition to writing essays and verses in Latin and Italian, he wrote an extensive practical treatise on ciphers and codes and one on the art of secret writing; he invented revolving disks for coding and decoding. He wrote books on human physiognomy, meteorology, and the refraction of light long before and perhaps to the bewilderment of Robert Hooke. There were other treatises on pneumatics, on the design of villas, on astronomy, and on distillation. He wrote and is said to have had staged a number of comedies and tragedies, popular at the time. Some of them were fountainheads to which later playwrights of the English-speaking world went for ideas. Wise men find the *fons et origo* of some of William Shakespeare's immortal works in the earlier works of Porta.

The *first* book of Natural Magick deals with "the causes of wonderful things." It is a straightforward discussion of the objects of natural philosophy. The *second* book, "on the generation of animals," is a potpourri of the most extravagant fables diluted by a few facts. Weird creatures resulting from the sexual congress (as they called it) of different species and classes of animals were listed with naive finality, the passionate conviction born of credulity. The inheritance of acquired characteristics was accepted as basic doctrine, not proved but accepted. Included is such useful miscellaneous information as an ancient preview of the watering of stock, with details of an experiment, whereby we may "procure in oxen a counterfeit show of fatness. . . . You take an Oxe well grown in years, and make a hole in his thigh, and blow wind thereby into him, and afterwards give him meat; he will show fat though indeed he be very lean." No lessons for Wall Street here!

The *third* book, on "The Production of New Plants," has much more fact but still a great deal of fancy. It approaches the problem of manufacturing new species from a kind of Luther Burbankian tossing of seeds and pollen to the winds and reaping the whirlwinds. This is heady stuff in the wintry time of seed catalogues—or even in summer. The *fourth* book of Natural Magick, "which teacheth things which belong to housekeeping, how to prepare domestic necessaries with a small cost, how to keep them when they are procured," deals with preservation of fruits and flowers. It gives many hints about simple domestic and agricul-

tural husbandry, with a large budget of casual suggestions. Many were part of the folklore of the time. Some survive in practice today. Methods for artificial incubation of eggs and their hatching "without a hen" are described in fairly modern terms. The incubator is as old as time. The *fifth* book, treating of "alchymy," is another mishmash of fact and fiction, running the range of what was known to the tinsmith, the goldsmith, and the silversmith but thence on to the most enticing suggestions for manufacturing gold out of baser metals. The *sixth* book gives further insight into the curious standing of "science" in a discussion "of counterfeiting of precious stones." It runs the gamut—from the manufacturing of colors to "substitution of various inferior metals and stones for those which are precious." The *seventh* book deals with an eternal natural wonder. It fascinates everyone today who is not oversophisticated and bored—the lodestone and the mysteries of magnetism. Despite our advanced mathematical comprehensions, bringing together in a "unified" field theory a simple statement which aims to comprehend all knowledge of mass and energy and substance—despite the fact that we have measured and named them—we do not actually understand magnetism and gravity much better than did the Otiosi. The use of the lodestone in curing domestic infelicity is perhaps only a trivial and passable exaggeration. The *eighth* book, "of physical experiments," deals with sedatives and all manner of drugs, including the sixteenth-century variety of knockout drops. Gangsters will learn little here. People interested in psychoanalysis will be interested in Porta's instructions on how "to cause several kinds of dreams." Urologists will be anxious to know what was the current method used "to bring away the stone," and dermatologists might want to know the procedures "against crab lice" and "against the chapping of lips" and "against the clefts of the fingers." Dentists could profit by learning how "to fasten the teeth." We all might be helped by remedies for the "head-ach," for pleurisy, for strengthening the stomach, preservations against the pox, antidotes against poisons, remedies for wounds, and such like. But this is not enough. Porta, anticipating by some centuries Munchausen's syndrome, has a section on how to counterfeit infirmities. He begins by stating "it hath been no small advantage to some to have counterfeited sicknesses that they might escape the hands of their enemies or redeem themselves for a small randsom or avoid tortures." There are even more detailed instructions on how to evade or avoid enchantments and fascinations and even a discourse on "some preservatives against love." The man included everything and then some. The *ninth* book is a really up-to-date vade mecum on beautifying women. I think few of our alert and original women today should skip the instruction for dying the hair, taking away wrinkles from the body, removing spots from the face, recoloring the face, and the sixteenth century's formidable and apparently unsuccessful attack on B. O. Sadly, there are no suggestions for that evil imposture and imposthume, today's version from Paris of the homosexual or asexual design the *sad sack*. Reading on, there is a very ungallant little section telling all sorts of tricks that can be played against women.

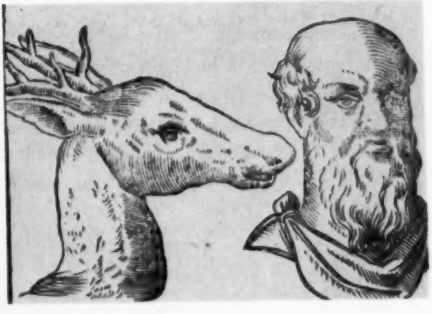
About the time when Porta's group of passionate natural historians began their activities, distillation was coming into popularity as a toy as well as an important domestic and industrial device. The *tenth* book is given over to the various processes of distillation and what may be achieved thereby. The *eleventh* book, "of perfuming," is very short but long enough to include instructions for adulterating various perfumes. The *twelfth* book deals with artificial fires, rockets,

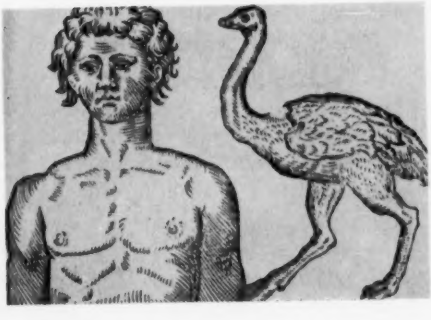
fire balls, and mysterious and magical things. Explosives then were for fireworks, not for killing. The *thirteenth* book deals with the tempering of steel and displays the fairly advanced state of that field of interest. Next, the chapter on cookery comes, somewhat surprisingly, before the one on how to catch living creatures with your hands—all about hunting, fishing, and fowling. Further discourse on secret and undiscovered notes, mysterious writings, "the burning glass," optics, statical experiments and levitation, and wind instruments. The most important observation contained in the book is in Chapter 17. This is a description of the camera obscura invented by Porta, employing a combination of convex lenses and a concave mirror to produce an erect image. He also called attention to the utility of the camera obscura in observing eclipses of the sun. Porta's belief that the eye was a dark chamber was fair enough, but he was mistaken in ascribing to the lens the role of a white screen, an error which was ultimately corrected by Kepler. Many other useful observations about lenses were recorded by Porta. Finally, and most appropriately, the last chapter is called "Chaos, where the experiments are set down without any classical order."

Here in brief is a glimpse of the state of learning in an age when the early morning mists were rising, seen in the light of the glistening of the dew, the happy freshness of wonder, when men accepted equally the wildest improbability and most evident fact with unquestioning enthusiasm and boisterous gusto, and received much else with fear. If in our day of sophistication we are more careful in our judgements, we must remember that wisdom may fray out in sophistry and that the yearning for security is apt to displace and deaden wonder and natural curiosity.

Epilogue to a Review

The oldest book I own is one by Gio. Battista Dalla Porta Napolitano, entitled "Della fisonomia dell'huomo." My copy was published by Tozzi, in Venice, in 1615. It belonged to my father, who obtained it because of its fascinating excursions into the borderlands between anthropology and magic. Porta's aim was to discover a recognizable connection between animals and man in physiognomy and in type. The book contains a combination of shrewd inference and the most arrant nonsense. The beastly qualities of man and the human qualities of animals are entrenched in an ancient tradition of fable and folklore and too often, in fact. Most languages are rich in words denoting analogies between man and animals, with emphasis on physical and mental traits, good and bad. This one is as greedy as a pig, or as dirty; another may be sheepish or graceful as a gazelle. The names of some animals have stood as verbs as well as nouns





slowly working their way into the vocabulary accepted of the schoolmarm. Sly as a fox, foxy, and to fox, are all readily recognized. Wolf has its own special connotations. Chickenhearted may indicate cowardice, and the word chicken is used by confused adolescents in a suicidal game played with cars. Some of Porta's drawings I reproduce here to show his shrewd imagination. We agree that the cow-faced man looks bovine. Whether the man looks leonine or the lion looks manly is more difficult to say. The long-nosed man is probably horse-faced rather than asinine. Perhaps the slanting face of the lad beside the pig indicates that he was porcine. The similarity of goat-like Pan, goat and man, is clear enough, though the resemblance of the bald-headed man to a deer is farfetched. In the bird figures, the aquiline nose, the eagle beak, the hooked bill or cocky nose, the long-necked ostrich-like man, and the man with shoulders of a pullet are good illustrations of what a little imagination may do.

As in the book on "Natural Magick," this book on physiognomy, the animal qualities of man and the human qualities of animals, is a mixture of fact and fancy, much more convincing at the level of folk similes and comparison than in a morphological classification within a biological system. Nonetheless, with his multitudinous activities and his remarkable accomplishments in so many fields, Porta illustrates the many-sided character of Renaissance man. If, in its first beginnings, science retained an enormous dead weight of the bookish erudition of antiquity, as experiments became understood and were repeated, man finally began his long trial at escape from the bondage of antiquity. In these books we have the beginnings of science which tries to see the world as it really is. We can enjoy them as examples of the early triumphs and failures of science. We need not accept anything just because it is written down and is traditional. But if we reject all history, good goes out with bad. Our rejection of antiquity has gone so far that we fail to profit by reading history. In neglecting it we subject ourselves to the risk of repeating every old error, the fate of all who are ignorant of history, according to Santayana.

This printing of Porta's "Natural Magick," old wine in a new bottle, should give a warm glow to any person who still preserves even a faint ember of curiosity or wonder. Even the teetotaler, the total abstainer from history, might savor this good nourishment without fear of intoxication and so escape his own self-imposed Prohibition.

WILLIAM B. BEAN, M.D.

Methodology of the Study of Ageing. Vol. 3. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc., for the Ciba Foundation. Price, $6.50. Pp. 202, with 47 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

With this volume, third of the Ciba Foundation Colloquia on Ageing, the intensive and extensive study of aging comes of age. While the diverse investigators and their many different approaches defy exact summary, this book deals with the life expectancy of wild animals and with somewhat comfortless data that deaths from all causes and pedestrian deaths from automobile accidents follow almost identical curves, that spaniels and wolf-hounds outlive dingoes, and that rattlesnakes lay increasingly more eggs as they get bigger and older until the old ones suddenly give up in a fit of aging or because of the frustrations of senility.

The difficulties of studying aging in cells and cell populations is illustrated graphically. Newer approaches to aging by such simple tests as stimulating the gums in animals and persons of various ages and measuring the response offers a promising and very simple way to study part of the problem. The sharp limitations of studies on human organ and system functions are brought out clearly, and the comparative values of the studies of the whole organism as against whole tissues are illustrated in detail. Geographical and racial differences are suggested by studies of aging in Africans; the genetic data on the aging of twins are evaluated. One of the critical studies, that of the human performance and its variation with aging, is still a relatively untapped but most important field for investigation, as is the effort to assay the intelligence and emotional responses of persons at different ages and the same person as he grows older. The general discussion was broad and interesting. In this book we begin to get a suggestion that with the serious emphasis on aging really useful facts may not only emerge but be brought together in a more coherent understanding of the entire problem which is so intimately connected with concepts of life, of dying, and of time. These our philosophy is just beginning to encompass, and we hope that it will be along sound lines.

WILLIAM B. BEAN, M.D.

Fat Consumption and Coronary Disease: The Evolutionary Answer to This Problem. By T. L. Cleave, M.R.C.P. Price, $2.50. Pp. 40. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

Here is a little 40-page book on sale for $2.50. The author endeavors to convince the reader that high fat consumption as a cause of coronary artery disease is effective only when natural fats are not consumed and the taste is not allowed to dictate the amount of fats eaten. While this is an interesting concept, there is absolutely no evidence set forth that is has any more validity than the average daydream. There is much discussion of the sophistication of foods. Obviously the author falls in among the compost people who believe that many of the ills and ails of man come from his oversophistication of foods. Though my own beliefs tend to follow in this general direction, I am aware of the almost infinitely complex requirements for getting evidence to bear on the problem and the infinitely painstaking, laborious, costly, and very long studies needed to provide clear evidence. While the author's thesis may be right enough, research by decree, even calling attention to the hope that elsewhere the author will make an attempt to demonstrate his thesis, no matter how valid this thesis may be, represents a strange departure from the ordinary factual presentation of science. Had the author entitled his book "Speculations on the Possible Evolutionary Answer to the Problem of Fat Consumption and Coronary Disease," he would have kept my interest from a continual process of dwindling throughout the book and leaving the sensation of driving on where the bridge was out. In an article which has only 38 pages of text, it seems ridiculous on almost every page in the first half of the book to refer to something that is coming in the second half, and in the second half to refer to things which have already been said in the first half. This tends to occupy a lot of space, as though the author were paid by the word. It renders even more obscure the opaque and turgid style in which one finds many sentences such as this: "We have already referred to the effects of physical exertion on fat consumption, so that it is comprehensible that coronary disease is less prevalent in those who experience much of the former." As with much of the rest of the book, what this means is anybody's guess. Don't bother with this one.

WILLIAM B. BEAN, M.D.

Old Doc. By O. H. Perry Pepper, M.D. Price, $3.75. Pp. 247. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

The life of every physician contains the matter for a novel, a biography, or an autobiography. In this book by Perry Pepper called "Old Doc" we have blended into a smooth unit elements of all three. This book purports to be the tale of Old Doc when retired from a full-time career as physician in a city hospital, recently widowed, and assailed by the intense loneliness of old age compounded by the loneliness of a big city. While the author wisely denies that any person living or dead forms the basis for the book, certainly Old Doc, despite the disclaimer and his different physical characteristics, is a good alter ego for Perry Pepper. While Old Doc chides his own garrulity, this charming book is not overloquacious. It abounds with lore of medical practice in times gone by, when the horse and buggy were being supplanted by the horseless buggy. Then the world seems to have been ever so much younger, tempers not nearly so violent, and the magnitude of our all-encompassing problems neither so ominous nor so imminent. One senses throughout the scholar's feeling for words which Perry Pepper has demonstrated so elegantly elsewhere; his sense of history and his participation in it, and his friendly familiarity with recent and ancient medical classics. There is much wisdom here for burgeoning doctors and very perceptive thoughts about the multitudinous reasons for success or failure in medicine. The discourse on practical jokes and especially William Osler's prodigious capacity for practical joking are very interesting but make such behavior no more intelligible for the victim while pleasantly delightful for the conspirator, remaining mysterious to mankind at large. Some excellent medical "whodunits" are dealt with happily. The chapter "Death of a Classmate" gives us one of the few outspoken essays on death in contemporary medical writings. Despite the fact that I do not agree with his entire position, it is stated with emphasis and clarity. Old Doc brings out a list of ten bedside books for the undergraduate or graduate physician to be compared with Osler's (1) Old and New Testament, (2) Shakespeare, (3) Montaigne, (4) Plutarch's Lives, (5) Marcus Aurelius, (6) Epictetus, (7) Religio Medici, (8) Don Quixote, (9) Emerson, and (10) Oliver Wendell Holmes' Breakfast Table Series. His own includes of Osler's only the Breakfast Table Series. It has Samuel Pepys, Cotton Mather, Benjamin Franklin, Jerome Cardan, Thomas Hodgkin, Benjamin Rush, and William Osler, with a very fine defense of his reasons why he has chosen them. I could find only eight of his list of ten. Perhaps Old Doc was slipping a little.

I can express my views about ten best books or ten best anything by saying that ten may not be nearly enough or may be too many. I should include classical medical texts and monographs, medical biographies and autobiographies, certain collected essays and papers, and then a miscellany of poems and prose which would get completely out of hand as mere bedside reading. Nonetheless Pepper's book is pleasant and stimulating. But not books only—frauds and fakers, administrative medical and military hierarchies, rare cases and the graces of family life are set forth with charm and warmth and fine perception. I can say in sorrow that people of the clinical skill, the humane warmth, and the scholarly views of Old Doc are passing from the scene. Whether their replacement by the brilliant scientist and the skilled laboratory man will be enough, only time can say. To show that Old Doc was only human and thus invoked the inalienable right to make mistakes, he attributed to John Hunter, the anatomist, the words of his less famous older brother William, who whispered just before he died, "If I had strength enough to hold a pen I would write how easy and pleasant a thing it is to die," rather than what Old Doc says: "If I but had the strength I would write how easy a thing it is to die." John Hunter's most famous quotation, of which I have found nearly two dozen variants, expressed his opinion about his own angina and hospital committees and administrators generally saying "My life is in the hands of any rascal who chooses to annoy and tease me," and he proved his point by dying abruptly after his temper had been provoked in a committee meeting. But such fly specks do not detract from a warmly humane picture of a vanishing era, set down lovingly, with pleasure and with grace.

WILLIAM B. BEAN, M.D.

Fundamentals in Cardiology. By John B. Wild, M.D. Price, not given. Pp. 83, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill. 1958.

It comes as a surprise to realize how little effort has been made to translate the extensive data obtained by the techniques of cardiac catheterization into the important approaches to

bedside medicine which they can illuminate so helpfully. In this book Wild has made the effort to simplify bedside teaching in a way that seems at first paradoxical, by adding complexities to a different subject. This always happens when we depart from the cookbook approach, where signs and symptoms have been learned as mere symbols rather than in terms of the dynamic mechanisms responsible. Wild achieves his goal of clarity and actual simplification by the employment of a series of charts beginning with the simplest concepts and adding additional features one at a time. Originally his method employed transparent and superimposable sheets so that the combinations could be studied in any sequence or combination. Though this is not an easy book to read, it is clear and straightforward. Even for one familiar with the concepts and problems, it presents difficulty only because of the inherent difficulty of the subject. It makes an excellent contribution to the modern approach to understanding disease of the heart on the basis of important information obtained with the measurement of intracardiac and intravascular pressures, combined with the traditional approaches of physical examination. Not only will this book help the student and house officer, but it should be of value to anyone who examines the heart.

WILLIAM B. BEAN, M.D.

Gout. By John Talbott, M.D. Second edition. Price, $6.75. Pp. 205, with 63 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

In our days of ultraspecialization, it is not unusual for one physician to become a connoisseur not only of a single disease but sometimes even of a fragment of a disease. In many respects Talbott has made gout his own particular property. Not only does he share this disease with many others but his special knowledge is founded upon a broad basis of clinical experience and wide knowledge of general physiology and environmental physiology. This second edition of his essay on gout is notable for combining a delightful historical flavor with the most up-to-date views about this distressing and still very refractory and irksome metabolic disease. We do not know the cause of gout, despite the fact that we have included it among the inborn errors of metabolism. Newer concepts about the metabolic pool of uric acid, its intermediary metabolism, the mechanisms whereby tubular blockade in the kidneys permit the excretion of uric acid, and many other aspects of the seemingly interminable problems connected with gout are dealt with lucidly. The author is a well-known expert with wide personal experience who has made many important contributions to the subject. The series of color illustrations and x-ray photographs adds conspicuously to the usefulness of the book.

WILLIAM B. BEAN, M.D.

Heart Disease and Pregnancy. By C. Sidney Burwell, M.D., and James Metcalfe, M.D. Price, $10.00. Pp. 338, with illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This fine book deals with the heart in pregnancy, heart disease in pregnant women, and especially pregnancy in women with heart disease. Burwell and Metcalfe have made a distinguished contribution to a field which until fairly recently was characterized by neglect, confusion, and error. As they point out in their historical review, Michel Peter in 1871 and again in 1874 discussed accidents that happened to pregnant women suffering from disease of the heart. He had observed five women with heart disease who got into trouble during pregnancy and was very pessimistic about the whole thing, saying that a woman should not become pregnant if she had heart disease, that if she had a child she should not nurse it, and that miscarriage usually occurred in pregnancy complicated by heart disease. One of his students, Auguste Berthiot, wrote his medical thesis at the University of Paris on pregnancy and disease of the heart. He was much distressed that he got absolutely no help from any of the classical medical or obsterical textbooks. These two French physicians actually seem to have broken the way for a study of the problem, which soon was taken up by Angus MacDonald, who wrote the first textbook on this subject, published by J. & A. Churchill in London in 1878. It was entitled "The Bearings of Chronic Disease of the Heart upon Pregnancy, Parturition and Childbed." He, too, took a pretty dim view of pregnancy in women with heart disease or heart disease in pregnant women. He observed that examination of the heart, especially its sounds, had confused clinicians, and that more attention should be paid to the functional capacity of the heart. The modern phase of understanding heart disease and pregnancy began in the efforts of Dr. Read, Dr. White, and particularly Dr. Burton

Hamilton, at the Boston Lying-In Hospital, where for nearly 40 years an extensive program of study of the dynamics of the circulation in pregnant women and the effect of heart disease on the normal course of pregnancy has been worked out in detail. Though Sir James Mackenzie wrote a textbook in 1921 emphasizing the importance of knowing the functional capacity of the heart, a good indication of the great advances since his day is seen when comparing his book with that of Burwell and Metcalfe. Jenson's book "The Heart in Pregnancy," published in 1938, gave a good general review of the situation but was quickly superseded by the text of Hamilton and Thompson entitled "The Heart in Pregnancy and the Childbearing Age," which opened up the contemporary modern period. This book was based on an experience with almost one thousand pregnant women with heart disease. In it was documented the very striking reduction in mortality of pregnant women with heart disease, much of which could be attributed directly to the authors' careful studies.

It is surprising that the circulatory aspects of the dynamics of pregnancy have had so little attention from obstetricians. Only in relatively recent times has any headway been made in our understanding of the normal circulatory changes of pregnancy and the important consideration of precisely how such alterations tax the diseased heart, what the special hazards are, and what should be done to prevent, moderate, or correct them. The first portion of this book is given over to a discussion of the maternal adjustments to pregnancy which are now established on a sound basis, though the material is probably less than in any comparable aspect of cardiology. Perhaps the most valuable part of the book is that dealing with specific diseases to which women in the childbearing age are liable. This is the major theme of the book. Rheumatic fever alone might have constituted a sufficient subject, since it is by far the most common heart disease which may disturb pregnant women. The entire problem is discussed in a masterful way from very extensive personal experience. There is a concise but thorough summary of what has been discovered and written by others. For particular patients and as a reference book, the sections on congenital heart disease, disorders of the heart beat, hypertension, preeclampsia, angina pectoris, myocardial infarction, bacterial endocarditis, less frequent types of heart disease, and the concluding chapters on syncope and neurocirculatory asthenia are extremely helpful. The contents of this book should be known thoroughly by all cardiologists and preeminently all obstetricians. At the same time, it will be of interest and value for internists and general physicians.

The introduction to each chapter contains an index for the chapter. A whimsical verse or quotation is at the heading of each chapter. Only in very rare spots is the writing redundant or awkward as in the use of hereby for herewith, discussion of persons who "underwent interruption of pregnancy," and a few other trivial specks. The index is only fair. For instance, there are at least seven references in the text to sudden death which I jotted down, not one of which is to be found in the index, but the table of contents and the headings for each chapter are so complete that this is a less serious fault than it would otherwise be in a splendid reference book, which is a model of its kind.

WILLIAM B. BEAN, M.D.

The Effect of Long Term Treatment with Dicoumarol in Myocardial Infarction: A Controlled Clinical Study. By Christopher Juel Bjerkelund. Price, $4.50. Pp. 212. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

This is a book-form publication of Supplement 330 to *Acta medica scandinavica.* The significance of the study warrants its appearance in book form for wider distribution in this country.

The study offers proof of the effectiveness of the Norwegian system of medicine in finding answers to difficult medical problems. Full time, for six years, was devoted to this study by Bjerkelund, an Assistant Physician to the Ullevål Hospital in Oslo.

Patients with myocardial infarctions admitted to the medical departments of the Ullevål Hospital from July, 1950, to July, 1953, formed the basis of the study. During the acute stage, all patients were treated with anticoagulants. One month later, the surviving patients were divided equally into control and treated groups. Only patients under the age of 76 were included, and the division was made on a ward basis. This method resulted in comparable groups. Two hundred twenty-seven patients were originally available. Twenty-six were eliminated from the study because of strong contraindications to anticoagulant therapy. There were finally available 119 suitable patients in the treatment group and 118 patients in the control group.

All patients were treated by the author in a cardiac clinic. Sympathetic understanding and thorough examinations were used to keep the control group intact. Placebo therapy permitting a "double blind" study was rejected by the author as not humane and not practical.

Patients were not excluded from the treated group for lack of intelligence or cooperation. Patients were given simple and repeated instructions. The close physician-patient relationship developed cooperation. During the first few weeks after discharge, prothrombin levels were determined weekly. Later the interval was prolonged to 10 days, and after 2 to 3 years, tests were made every 3 to 4 weeks in some patients with stable prothrombin times. Prothrombin times were kept well below 30% in the majority of patients. The combined effect of prothrombin and proconvertin was measured with use of Owren's method.

The results were clear. New infarction occurred in 26 of the treated patients (22%) and in 47 of the control group (40%). In the treated group, 9 of the 26 recurrences were fatal, and in the control group 21 deaths occurred among 47 recurrences. At autopsy examination, evidences of coronary thrombosis were noted twice as frequently in the control group (58%) as in the treated group (26%). There were 32 hemorrhages of clinical significance in the anticoagulant-treated group and 9 in the control group. At the time of hemorrhage, about one-half of the treated patients had prothrombin times below 10% of normal.

Analysis of the results gives a practical guide to therapy. Only in patients under the age of 60 was long-term anticoagulant therapy of statistical significance, and it was of significance only for the first year after the infarct. A greater effect of therapy was demonstrated for patients with a single infarct and for those with an uncomplicated clinical course during the acute phase of the illness. There was no difference in the course of angina pectoris between patients in the control and treated groups.

The results of the study are consonant with pathological data and other considerations of myocardial infarction. The effectiveness in preventing infarction was slightly less than 50%, a figure corresponding to the estimated incidence of thrombosis causing infarction. Recurrences in the treated group did not relate to prothrombin levels. In older patients, with presumed generalized coronary sclerosis, anticoagulant therapy was not so effective. The same state of advanced sclerosis may exist in patients who have had many previous infarcts. Anticoagulant therapy would, likewise, not be expected to alter markedly the course of some patients with heart failure and cardiac enlargement resulting from myocardial infarction. Neither would those anginal attacks caused by functional circulatory events be modified by therapy. The lower mortality in patients in the treated group with infarctions is not easily explained, and the author does not attempt it. Similar reductions in mortality have been noted in other series.

This study, carefully and critically performed, constitutes a major step forward in the thorny underbrush of the problem of long-term anticoagulant therapy related to myocardial infarction. While not the final answer, it gives the best basis for guidance to date.

ANDREW KERR JR., M.D.

Die Bluteiweisskörper des Menschen: Untersuchungsmethoden und deren klinisch-praktische Bedeutung. F. Wuhrmann und Ch. Wunderly. Third edition. Price, $13.00. Pp. 499, with 179 illustrations. Benno Schwabe & Co., Basel 10, 1957.

This well-written and richly illustrated book emphasizes, as indicated in the subtitle, correlation of changes in plasma proteins with disease states. Primary attention is given to paper electrophoresis as method of analysis, in combination with turbidity and flocculation reactions of serum.

In the preface, the authors explain that space restrictions preclude discussion of the closely related problems of the hemoglobins, coagulation, and lipoproteins to a significant extent. Chapters on paper chromatography and spectrophotometry which had been part of the previous (second, 1951) edition were omitted from the new book because, on the one hand, the authors found that analysis of serum proteins by serologic methods, including immunoelectrophoresis, was, in part, replacing those methods; on the other hand, the latter were well covered in recently published handbooks. No explanation is given for the almost complete lack of attention to circulating enzymes, which are assuming an increasingly prominent role in physiologic and clinical investigations. Only passing mention is made of esterases, amylase, and phosphatase; transaminase and many other known serum enzymes are totally excluded from the pages of the book.

The first chapter, entitled "Chemistry of the Plasma Proteins," presents a lucid discussion of the structure and composition of these proteins, followed by short treatises on the physico-

chemical properties of albumin, the globulins (including carbohydrate-proteins), fibrinogen, C-reactive protein, and the properdin system. Subsequently, atypical proteins (paraproteins) are considered, including cryo- and macroglobulins and the Bence Jones proteins and the functional effects of the total serum proteins (colloid-osmotic pressure).

After a brief chapter on qualitative tests (xanthoprotein, biuret) and quantitative methods (refractometry, specific gravity, Kjeldahl), a detailed description of some of the main analytical techniques follows: salting-out, Cohn fractionation, electrophoresis (including the three varieties, free, immunologic, and paper), and ultracentrifuge. The last-mentioned procedure is discussed only with regard to fundamentals and principles of technique; the authors confess the lack of experience of their own with this procedure.

Chapter 4 is devoted to a description of technique and clinical application of a few "clinical-chemical methods," with particular reference to sedimentation rate, Weltman's $CaCl_2$ heat-coagulation test (and a refinement of this test called "nephelogram"), and several of the well-known turbidity and flocculation reactions in serum, such as Takata-Ara (with various modifications), cephalin cholesterol flocculation, thymol, cadmium sulfate, ammonium sulfate and zince sulfate turbidities, formol-gel reaction, and the "test for lability" of proteins involving dilution of serum with distilled water.

Much space is devoted to these serum reactions in the ensuing two chapters, which constitute nearly two-thirds of the entire book. In the first of these two chapters (Chapter 5, "Clinical Importance of the Plasma Proteins"), nine prototypes of plasma protein abnormalities are described, designated as *Reaktionskonstellationen* or *Konstellationtypen*. Each of these "constellations" is based upon eight routine tests: sedimentation rate, $HgCl_2$ reactions (Takata-Ara), cephalin, thymol, cadmium, total protein, Weltman band, and paper electrophoresis; they represent these clinical groups of disorders: (1) type of acute inflammation, (2) type of subacute to chronic inflammation and proliferative processes, (3) type of hepatitis, (4) hepatic cirrhosis, (5) obstructive jaundice, (6) nephrotic syndrome, (7) malignant neoplasm (without significant involvement of liver), (8) plasmacytoma of the γ-globulin variety, and (9) plasmacytoma of the β_1-globulin variety. The significance and interpretation of these procedures in clinical practice is outlined in much detail. A "small reaction constellation," the Weltman plus the cadmium sulfate reactions, is suggested as useful for estimating increases of the various globulins. An extensive outline of the major groups of disorders and of numerous individual diseases follows, in which changes in electrophoretic pattern and in the allied serum tests are correlated with pathophysiologic alterations as observed in the respective maladies.

The next chapter, entitled "Clinic of the Dysproteinemias and Paraproteinemias" and introduced by a dissertation delving into the semantics of plasma protein alterations (dys-, pseudodys-, para-, patho-, hypo-, hyper-, normo-, euproteinemias) affords an inverse type of presentation: the three main plasma fractions—fibrinogen, globulins, and albumin—are listed, with functional and diagnostic interpretations assigned to each of the alterations of those fractions. Obviously, there is much overlapping of information with the preceding chapter. Among changes in fibrinogen concentration, the clinical syndrome of in vivo defibrination is not included. Much space is devoted to certain paraproteinemias: plasmacytoma (including a tabulation of free-electrophoresis diagrams of the sera of 100 patients), Waldenström's macroglobulinemia and hyperglobulinemic purpura, and agammaglobulinemia. The recently discovered congenital analbuminemia is mentioned and illustrated.

The last chapter (Chapter 7) deals briefly with the origin and formation of the blood proteins, focusing on the liver and the reticuloendothelial system (including plasma cells) as the main sources.

I was struck by the strong emphasis in the book on empirical "constellations" of laboratory tests as practical means of clinical diagnosis. The categorization employed appears somewhat artificial; the approach to the various "constellations of tests," overly mechanistic, and their description is, at times, long-winded. The diagnostic system offered here may appeal to the dogmatic "diagnostician" rather than to the student of this complicated and ever-changing biological process called "disease." Similarly surprising is the attention and space devoted to "nonspecific" serum reactions, at a time when great strides are being made toward specific biochemical identification of metabolic and structural lesions. Turbidity and precipitation tests are highly useful in initial screening and, when properly selected, frequently of much assistance in differential diagnosis, but the recommendation to utilize them routinely in form of a rigid "constellation," battery, or profile of tests does not make for effective teaching or good medical practice. The prediction is probably safe that these nonspecific tests will

gradually move into the background as more specific methods of analysis, such as electrophoresis, serologic procedures, and enzyme determinations, are taking over. Indeed, it is in this sense that the authors consider paper electrophoresis to be equal in practical importance with the routine blood cell count.

Aside from the limitations and shortcomings mentioned, the book offers a great deal of well-organized information on the subjects which it is designed to cover. It is particularly instructive as a source of methodology of paper electrophoresis and of variations of electrophoretic plasma components in disease; the large number of photographs of electrophoretic patterns and curves, amplified with exhaustive legends and case reports, make this book a veritable atlas of paper electrophoresis. Moreover, it represents a compilation of valuable references, particularly of the foreign literature, not readily accessible to American students of the subject. Last but not least, the book reflects the authors' wealth of clinical and laboratory experience and transmits it in a readily understandable and systematic form. For all these reasons, it will prove to be very useful to many an internist, clinical pathologist, and clinical chemist.

EMANUEL E. MANDEL, M.D.

Medicine in Chicago: 1850-1950. By Thomas Neville Bonner, Ph.D. Price, $5.00. Pp. 302, with illustrations. American Historical Research Center, 816 State St., Madison, Wisc., 1957.

If history may be considered the biography of great men, then the medical history of a country consists of its local, city, regional, and state histories. There are but few good histories of medicine dealing with cities and very few, indeed, dealing with the American cities. Boston and Philadelphia have fairly good formal medical histories. A few others, notably Cincinnati, have their past well recorded by medical historians. Indeed, Daniel Drake's epochal volumes dealing with the diseases of the interior valley of North America managed to include a broad ecological approach to medicine as well as medical history at the same time, and Drake's charming little book with its two discourses on the beginnings of medicine in Cincinnati has become a collector's item. Nonetheless, regional histories of medicine are few and are likely to be second-rate affairs.

Chicago is not the newest of the great cities in this country. Its medical history, being almost coterminous with its great growth and the development of modern medicine in America, gives us a mirror of medical progress over the past one hundred years. Thomas Bonner has told the story in a pleasantly written and thoughtfully analyzed history, interesting for anyone concerned with American medicine, medical history, or Chicago. In this lusty city Murphy, Senn, Hektoen, Herrick, Fenger, Nathan Smith Davis, and others not only guided the local history and the community but were influential in greater medicine in the country.

In this book are interesting descriptions of the relationships between white and Negro physicians; the rise and coming of age of full-time medical teaching; the growth of the American Medical Association; the development of public health work, upon which depended the growth and flourishing of cities; the more recent indications of the decay of cities with the growth of suburbia; the origin, the development, and the changing face of modern hospitals, and the sociomedical problems of the last century and this century. A description of medical societies, strangely enough, does not mention the important role of research societies, such as the Central Society.

Reflecting as it does the growth of medicine over the last 100 years, this book provides a miniature history of medicine in the Western World of our time. The transformation of a pioneer village with a tiny little fort, the foundations of which are marked out on the sidewalk of Michigan Avenue, is emphasized by the giant skyscrapers of the lake shore. The infinitely complex problems of preserving the health of a big city, which for a long time had a closely intermeshed water and sewage system in the lake, the heroic and bombastic medical figures with their Paul Bunyanesque raucousness have all disappeared in the emergence of a great city, still with its infinity of problems but one in which medicine of a high standard is taught, where research goes on in innumerable laboratories and medical schools, and where one can find the highest order of medicine practiced. The scholar, the medical historian, and any physician interested in the history of medicine or the history of the Middle West will have much pleasure in reading this book.

WILLIAM B. BEAN, M.D.

The Pharmacology of Psychotomimetic and Psychotherapeutic Drugs. Conference Chairman, Seymour S. Kety. Published in *Annals of the New York Academy of Sciences*, Vol. 66, Art. 3, pp. 417-840. Price, $5.00. Pp. 424. New York Academy of Sciences, 2 E. 63d St., New York 21, 1957.

This book was the result of a conference on the pharmacology of psychotomimetic and psychotherapeutic drugs held by the New York Academy of Sciences, Section of Biology, on April 12, 13, and 14, 1956. It concerns itself with clinical, biochemical, and neurophysiological effects of psychotomimetic agents, serotonin, and psychotherapeutic drugs. So much material is presented that one can only discuss a few of the more pertinent articles.

Research in psychiatry has dramatically changed in a few short years from that concerned only with psychodynamics to studies in cerebral metabolism, the model psychoses, and the tranquilizing drugs.

Similarities between behavior produced by lysergic acid diethylamide (LSD) and schizophrenia have prompted a thorough investigation of psychotomimetic agents. Of interest is the fact that despite the gross personality changes produced by LSD it has been most difficult to define its mechanism of action. A paper by Hoagland indicates that LSD may modify oxidative phosphorylation. Sokoloff showed that the drug caused no alterations in cerebral oxygen consumption. The effect of the drug on the electrical activity of the brain was not at all consistent. In one interesting paper Apter and Pfieffer suggest that the hallucinations produced by psychotomimetic drugs may well result from peripheral effects on the retina rather than from central effects on the brain. Marazzi related these drugs to adrenergic agents in general, such as epinephrine and arterenol, and proposed that their mechanism of action was related to their ability to inhibit synaptic conduction. Osmond, Hoffer, and Hoagland have hypothesized that an inborn metabolic defect in schizophrenia produces a schizophrenogenic end-product of epinephrine degradation.

The role of serotonin as a neurohumor mediator is thoroughly reviewed. Wooley and Shaw theorize that mental illness is related to either an excess or a deficiency of serotonin in the central nervous system. They propose that serotonin produces periodic contractions of the oligodendroglia, which result in a stirring action. With a deficiency of serotonin this stirring action is inhibited and essential metabolites are circulated too slowly to supply the normal requirements of the brain.

The supposition that LSD produces psychosis by inhibition of serotonin is disputed by some authors, inasmuch as other ergot alkaloids also inhibit serotonin but do not produce psychosis.

Margolis exhaustively assays the impact of tranquilizers on clinical psychiatry. Their early promise has not fully materialized, but their contribution to the treatment of certain kinds of patients cannot be denied. Meprobamate is considered effective in the control of neurotic anxiety and tension states. The phenothiazine derivatives and reserpine are of greater value in illnesses associated with more disorganizing kinds of anxiety, allowing for diminished use of insulin and electrotherapy. None of these drugs is of value in the amelioration of depression, and reserpine and chlorpromazine at times precipitate depressive symptoms.

There are in this review a number of papers on the effects of drugs on conditioned behavior in lower animals. The book indicates greatly accelerated research in the area of biological psychiatry directed at more fundamental understanding of brain mechanisms and their relationship to mental illness. This book certainly deserves reading by those interested in following this area of medical progress.

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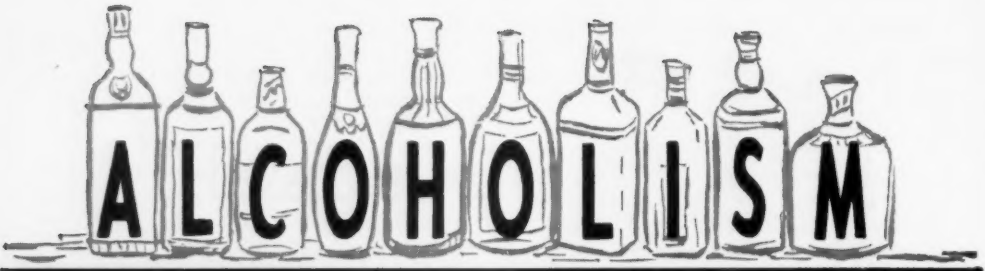

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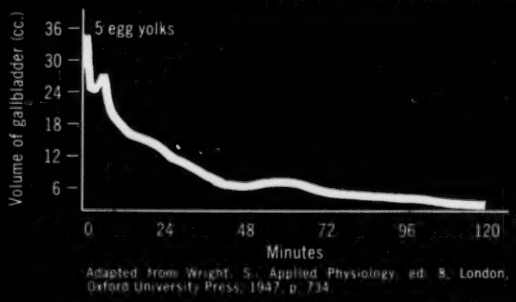

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2. Shehadi, W. H.: Am. J. Gastroenterol. 28:236 (Sept.) 1957.

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